A practical guide to the newer remedies / by J.M. Fortescue-Brickdale.

A PRACTICAL GUIDE TO THE NEWER REMEDIES

J. M. FORTESCUE-BRICKDALE

A PRACTICAL GUIDE TO THE NEWER REMEDIES

A PRACTICAL GUIDE

TO THE

NEWER REMEDIES

BY

J. M. FORTESCUE-BRICKDALE, M.A., M.D. Oxon.

Physician to Clifton College; Assistant Physician to the Bristol Royal Infirmary; Lecturer on Pharmacology in the University of Oxford; and Clinical Lecturer in the University of Bristol; Joint Author of "The Chemical Basis of Pharmacology."

"There is no catholicon or universal remedy."

BRISTOL: JOHN WRIGHT AND SONS LTD.

London: Simpkin, Marshall, Hamilton, Kent & Co. Ltd.

1910

JOHN WRIGHT AND SONS LTD.,
PRINTERS AND PUBLISHERS, BRISTOL.

PREFACE

THIS book does not concern itself with patent medicines or secret remedies, nor does it deal with therapeutic methods as such. It is merely an attempt to pass in review the newer drugs (mainly the products of synthetic chemistry) the composition of which is published and whose pharmacology has been more or less accurately ascertained. In order to give a practical value to the work, the various drugs described have been criticized and compared, and the experimental and clinical evidence for and against the usefulness of each has been carefully weighed, whilst in all cases directions are given as to dosage and the usual mode of administration.

Every care has been taken to secure accuracy; but, as in a work of this kind some minor errors are almost bound to remain undetected, the author will at all times be most grateful to those of his readers and critics who will be good enough to indicate any such as may come under their observation. In the matter of orthography, a

uniform method of spelling the names of chemical and pharmacological substances has been adopted, as far as possible in accordance with their etymology; but here again the author is conscious of the fact that occasional lapses are most difficult to avoid. Proprietary names have, of course, been spelt as their inventors direct.

Where official remedies are mentioned, the corresponding preparations found in the *B.P.* and *U.S.P.* have in all cases been stated.

In conclusion, the author desires to return his sincere thanks to those friends and colleagues who have kindly favoured him with their help and suggestions during the preparation of the work, and to the Publishers for the unfailing courtesy and care with which they have carried out his wishes and intentions in its production.

J. M. F.-B.

University of Bristol,

September, 1910.

CONTENTS

CHAPTER V

CHAPTER VI

CHAPTER VII

CHAPTER VIII

A PRACTICAL GUIDE TO THE NEWER REMEDIES.

INTRODUCTION.

THE aim and object of medical training appears to the author of this small book to be the proper equipment of a body of conscientious workers for the prevention and cure of disease. As regards the prevention of disease, notwithstanding the immense advances which have been made in this direction during the past twenty or thirty years, not only by the efficient organization of the Public Health Service under a remarkably capable body of medical officers, but also by investigations undertaken in the laboratory by many of the foremost scientific physicians of the age, it can hardly be said that this covers more than the smaller portion of the medical field. In the present state of our knowledge, the number of diseases to which prophylactic or preventive measures can be applied, is comparatively small when compared with the total number of pathological conditions which are liable to endanger life or jeopardize health. It is to the cure or alleviation of disease that the majority of medical men must, for the present, devote the greater part of their attention

during their professional career : it is therefore not a little curious, that the average medical student should be required to devote such a small portion of the curriculum to acquiring a knowledge of therapeutics and pharmacology.

Although the present writer would be the last to deny the importance to the student of medicine, both of a general scientific education and of a thorough knowledge of those fundamental sciences upon which rests the superstructure of the *ars medendi*, yet he does sometimes feel that too much time is now spent on detailed preliminaries, to the exclusion of those all-important practical subjects, upon a thorough knowledge of which his future success in his profession will, to a great extent, depend.

The result is that, in the time at his disposal, the clinical teacher can hardly expect to do more than impart to his students the elements of diagnosis and prognosis ; on the surgical side much time has necessarily to be spent in acquiring an elaborate technique ; while on the medical side the methods of diagnosis, both chemical and physical, become yearly more numerous and more complicated, so that at the end of his training, the student's notion of treatment is very often confined to a few vague therapeutic generalities, supported by a comforting reliance on the *vis medicatrix naturæ* and a firm belief in the policy of masterly inactivity.

Not many years of general practice, however, even in this age of scepticism, are needed to convince him that the public take quite a different view. As a

rule, he finds that a doctor is regarded as a person who is, humanly speaking, competent to heal the sick, which function he is to perform by means of certain detailed directions as to the diet, rest, and general surroundings of the patient, and also by the prescription of certain remedies to which, oddly enough, most people still attach considerable importance. He then finds that the knowledge, somewhat laboriously acquired, of the methods of recognizing crude official drugs, is, even if it is still retained, of singularly little use to him. Even a detailed acquaintance with the ingredients of many pharmacopœial pills, or the basis of various ointments, stands him in little stead. Fearful lest his recollection of incompatibles should be dangerously imperfect, he hesitates to embody what knowledge of drugs he does possess in a prescription, and the crowning difficulty comes when the patient mentions the name of a much-advertised proprietary article which he says has been successfully prescribed for a friend, and asks the doctor its composition, and whether it would not be beneficial in his own case.

It seems to the present writer that the medical curriculum is, on the whole, insufficiently elastic. As the wave of scientific and medical knowledge advances now at one point and now at another, it ought to be possible so to regulate the requirements of examining bodies that the student's knowledge and training should periodically adapt themselves, so as to take the fullest possible advantage of that special line of progress along

which scientific thought is travelling for the time being.

The writer has elsewhere expressed the opinion (which he holds most strongly) that the study of pharmacology should be given more serious attention, alike by the student and by the examining bodies; and it is with no little satisfaction that he has recently noted signs of a more general appreciation of this point of view. Pharmacology is, of course, merely a grouping together of certain facts for purposes of practical convenience and utility; it is not a science in the same sense that astronomy or chemistry are sciences. It depends, therefore, for its proper acquisition, on the knowledge of several other sciences, and the most notable among these are undoubtedly physiology and chemistry, inorganic and organic. Pharmacology should therefore be presented to the student as soon as he has acquired a sufficient knowledge of these two preliminary subjects, and they in their turn should be so taught as to render their relationship to pharmacology clear and easy. Especially in the case of chemistry can this be done; and by a judicious selection of examples and experiments, a considerable saving of time and mental effort on the student's part may be accomplished. He should, then, enter on his clinical studies with a knowledge of the main actions and the chemical characters of the principal drugs; ready to weigh in a critical spirit the evidence of their applicability to the morbid conditions of which he has to learn, and able to recognize that most

valuable practical expedient, empiricism, for what it is, and to be ever on the alert for fresh increases in knowledge which shall render its dominion over medicine less and less extensive and arbitrary.

It is, of course, with reference to actual cases and in this way alone, that the art of therapeutics can be taught; but while desirous that clinical teachers should give more time to this very important branch of medical knowledge, the writer is convinced that much of this time would necessarily be wasted unless the student had previously acquired a sound working knowledge of pharmacology. The intricacies of pharmacy and the disjointed details of materia medica are not at the present day any essential part of the medical man's mental equipment. Doses should of course be learnt, in order to give freedom in the use of remedies, but this must largely be in connection with the practical treatment of the sick, and need never be spun out into a mere matter of *memoria technica*. Of the many preparations in the pharmacopœia, but a few need be studied in any detail, for the success of the practitioner will depend, not upon the possession of many weapons, but upon the degree of skill with which he can use a few.

At the present time, the path of the medical man who has been educated to that pitch of pharmacological and therapeutic ignorance demanded by the examining bodies in this country, is made easier for him to a great extent by the gratuitous and often strongly-worded advice which is showered upon him by the manufacturers of chemical products, drugs,

and proprietary articles of all descriptions. Good and bad, old and new, powerful or indifferent, all are brought to his notice in the same way, accompanied by accounts of equally successful clinical trials, and often by a few chemical and physical descriptive details which his want of knowledge of these subjects makes it impossible for him properly to understand. When to this is added the fact that the trade names, at any rate, of many of these substances are known to the public, and as "new" and "scientific" remedies are ardently desired by them, it follows that the practitioner is forced once more to take up the invidious position predicated for him of old, of pouring drugs of which he knows little into bodies of which he knows less.

Until a considerable reform has taken place, therefore, in the teaching to medical students, of pharmacology, therapeutics, and the cognate science of chemistry, the writer hopes that this little work may be found of some use to those who have recently entered on their professional duties. Its scope, and also its limitations, will easily be gathered from a glance at the table of contents, while the index, which, it is thought, has been made fairly exhaustive, will render reference to any particular substance or subject comparatively easy.

No attempt has been, or indeed can be, made to render a book like the present absolutely exhaustive; the reader need only refer to such a bare catalogue of drugs as Riedel's "Mentor," to see how impossible and useless such a task would

prove. A large class, for instance, of so-called new drugs are merely mixtures of old and well-known remedies, or loose chemical combinations of the same, dignified with an attractive trade name and backed up by elaborate advertisement.

The large class of drugs derived from animal extracts of various kinds has also been excluded; a few active principles, the chemical constitution of which is more or less accurately known, have indeed been discussed, but only when their physiological effects are sufficiently definite. Sera and vaccines form a subject by themselves, of ever-increasing importance and complexity; they have not been included here, largely owing to the fact that an excellent handbook on the subject has been already published, and should be in the hands of every careful physician.

All that is aimed at here is to give some account of the properties and dosage of the principal new drugs in each class, and to indicate their relative and collective value as accurately as possible by reference to clinical experience, laboratory experiment, and a study of the literature.

In especial, the writer has, throughout the book, desired to give a practical value to the information it contains. Thus the dosage, and a short account of the appearance and solubility of each compound, is inserted, and as little as possible of a purely theoretical character has been allowed to find a place. Both the Metric and Imperial weights and measures have been given throughout, except in the case of a few

drugs which are used hypodermically, and practically always in such percentage solutions as can easily be calculated from the metric system. Subjects such as the modern methods of anæsthesia have been treated from the point of view of the general practitioner, and not that of the specialist, who would naturally consult the larger treatises and original authorities. For the benefit of those who may care to make this small work an introduction to more extended study, references have been given to all authorities quoted, and where original papers were not available, to abstracts or quotations in more easily accessible journals.

The author is more than sensible of the many imperfections and shortcomings of his work, but he trusts that there is still some measure of usefulness left to it, and that it will be a frequent if humble adviser in the hands of some of his junior professional brethren.

CHAPTER I.

IODINE :—(I.) Iodoform substitutes ; (II.) Substitutes for the Alkaline Iodides. BROMINE :—Substitutes for Potassium Bromide. SULPHUR :—(I.) Ichthyol and its substitutes ; (II.) Thiosinamine and its substitutes.

IODINE.

THE recently introduced iodine compounds are all practically intended to replace either iodoform externally or the alkaline iodides (potassium iodide, etc.) internally. A very large number of these compounds exist, and are on the market ; but few present any advantages over the older drugs ; and as their practical application and therapeutic indications are all similar, their description need not occupy much of the reader's time. The action, in both the external and internal remedies, is due to the liberation of the iodine ion and its effect on micro-organisms or tissue cells.

I.—IODOFORM SUBSTITUTES.

There are four main objections to the employment of this valuable drug, which the manufacturers of synthetic remedies have set themselves to overcome in devising substitutes.

1. It has an unpleasant and very penetrating odour, even when present in minute quantities.

2. It cannot be sterilized by heat, and is not itself aseptic.

3. It is liable to cause dermatitis.

4. It is sometimes absorbed in large quantities and sets up symptoms of general poisoning.

To obviate these objections, two classes of derivatives have been put on the market: (*A*) Those which owe their antiseptic action to the fact that, like iodoform itself, they liberate iodine when in contact with body fluids; and (*B*) Those which, though containing iodine, do not liberate it under these circumstances, and owe whatever antiseptic power they may possess to other causes.

A.—This class comprises two subdivisions: (*a*) Those which contain iodoform itself; and (*b*) Those which contain some other derivative in which iodine is but loosely combined.

Subdivision (*a*).—In this must be placed the various substances in which iodoform is mixed with some strongly-smelling body in order to conceal its own odour. Coffee, tar (*iodoformum bituminatum*) and coumarin have been used for this purpose, but the result is never satisfactory, as not only are the other objectionable features of iodoform uninfluenced, but even the odour is not entirely covered, as the added substance tends to lose its own smell in process of time.

Many French preparations are bodies of this sort, and apparently enjoy a certain popularity.

Iodoformin is a chemical compound of iodoform and hexamethylene tetramine (urotropin). It is a

powder, insoluble in water, possessing practically no smell, and containing 75 per cent of iodoform. It is, unfortunately, easily decomposed by moisture, so that when exposed to the air the odour of iodoform soon becomes apparent.

Iodoform has been also combined with inactive bodies such as albumin. **Iodoformogen** is a very fine, yellowish, almost odourless powder, insoluble in water, containing 10 per cent iodoform. It can be heated to 105° C. (219° F.) for some time, and thus sterilized without decomposition. It is usually employed undiluted, as the amount of iodoform it contains is but small. Mixed with equal parts of boracic acid powder, it may be used as a snuff.

Eka-iodoform is an addition product of iodoform and paraform (a polymer of formaldehyde). It has the iodoform odour, but the presence of the paraform is said to render it sterile.

Subdivision (*b*).—Contains a large number of bodies of more or less value.

Iodoformol is a hydriodide of ethyl-hexa-methylene-tetramine (ethyl-urotropin); it occurs as yellow needles or a harsh odourless powder closely resembling iodoform. It is insoluble in water and alcohol, and melts at 128° C. (262·4° F.). It is probably dissociated into hexamethylene-tetramine and hydriodic acid, the latter yielding free iodine. It is a powerful antiseptic. Its disadvantage is that, like the corresponding substance, iodoformin, it is too easily decomposed, with the production of the iodoform odour.

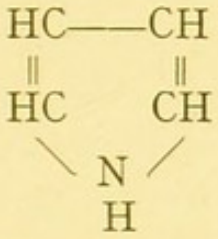
Iodyloform is a yellowish-brown, odourless powder, insoluble in water, alcohol, and ether, composed of iodine and gelatin. It is said to possess considerable antiseptic power. **Iodeigon** is an albumin compound, insoluble in water, and **eigon-sodium** and **pepto-iodeigon** differ from it in being soluble; they contain 15 per cent iodine. **Iodcasein** is composed as its name implies. It is a yellowish powder insoluble in water. **Iodotannol** is apparently a mixture of iodine and tannin.

Besides these bodies, there are several other iodine-containing substances of a totally different type, chemically, to iodoform, but resembling it in liberating iodine under similar conditions. **Di-iodoform** is a yellow, almost odourless, insoluble powder. Its composition is represented by the formula C_2I_4, and it is therefore ethylene tetra-iodide. It contains 95 per cent iodine. It is too easily decomposed for practical therapeutic purposes. This is true of all aliphatic iodine compounds intended to replace iodoform.

Aristol (46 per cent I) or annidalin is a thymol derivative; it must not be exposed to light or heat, and is prescribed as 5 to 10 per cent ointment in any ordinary basis. **Europhene** (28 per cent I) is a cresol derivative. Both are yellowish or reddish powders; the last named does not keep well in presence of moisture, and is used either mixed in equal parts with boracic-acid powder, or as a 10 per cent ointment in any suitable basis, being soluble in oils and fats; it must be prepared without heating.

The salol derivative stains the skin and linen. **Traumatol** (54 per cent I) which is an iodo-cresol, has a similar disadvantage. It is a fine violet-red, amorphous powder, insoluble in water, soluble in dilute alkalies. All are somewhat expensive preparations.

Iodol, the earliest of the iodoform substitutes, and in some ways the best, is a pyrrhol iodide. Pyrrhol is a five-membered ring, containing nitrogen,

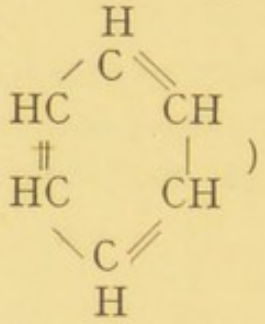


and when four hydrogens are replaced by iodine ($C_4I_4.NH.$) a brownish white, odourless, crystalline powder results, containing 89 per cent I. It is insoluble in water and can be decomposed by heat, giving off fumes of iodine.

An ointment containing 5 to 10 per cent iodol may be prescribed, and in gynæcological practice 1 part of iodol may be dissolved in 16 parts of alcohol and 34 of glycerin, and used on a tampon. The derivatives of iodol (e.g., *iodolene* with albumin, *caffeine iodol* and a compound with hexamethylene-tetramine) have no special advantages, and as they are more stable are less efficient as antiseptics.

B.—This class is most instructive from the pharmacological point of view, as it shows how substances may obtain an entirely baseless reputation,

owing to the fact that the outlines of the pharmacodynamic action of drugs are not sufficiently taught in the medical schools. Bodies belonging to the aromatic or benzene series (i.e., having somewhere in their structure a 6-carbon ring

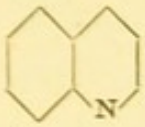


may contain iodine either *in the ring*, that is directly united to one of the carbon atoms in place of a hydrogen, or *in a side chain*, that is attached outside the ring, and only indirectly joined to one of the carbon atoms. In the former case the compound is too stable to give off iodine as does iodoform, but in the latter case iodine is given off. The former class of compound, though it contains iodine and may manifest antiseptic properties, cannot in any true sense be termed an iodoform substitute.

Iodofan is an addition product of formaldehyde and iodo-dioxybenzene ($C_6H_3.I.(OH)_2$) in which the iodine is in the ring. It is a reddish-yellow, odourless, crystalline powder, and may be employed as a dusting powder, or as an ointment with yellow vaseline. It is insoluble in the ordinary reagents, but decomposed by wound secretions, with loss of its red colour. An iodoformal is said to result.*

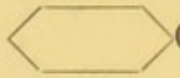
* Piokowski, *Berl. klin. Woch.*, Mar. 20, 1907.

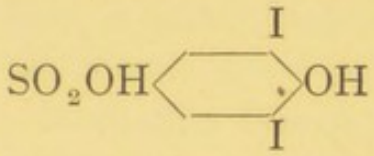
Loretin is a quinoline derivative, and is a yellow, tasteless, insoluble powder of considerable antiseptic value. **Griserin** is a mixture of loretin and sodium bicarbonate. **Vioform** is also derived from quinoline

(). It is a yellowish powder, without taste or odour, and insoluble in water. It may be sterilized by heating to 100° C., but higher temperatures decompose it.

Losophane is a cresol derivative containing 80 per cent iodine. It is apt to produce considerable irritation when applied to the skin. It has been employed dissolved in oil as a parasiticide. **Sanoform** (6·2 per cent I) is a salicylic acid derivative, soluble in vaseline and collodion. It is used as a dusting powder or a 10 per cent ointment; is non-irritating, odourless, and non-poisonous, and has an antiseptic action. **Isoform** (*p*-iodo-anisol) is a ring compound containing a group IO_2, which is thought to act like a peroxide, and so to be antiseptic. It is an explosive substance (at 225° C.), and is used with an equal part of calcium phosphate, or as a paste with glycerin. It smells strongly of anise. It is non-irritant and non-toxic, but otherwise has no special advantages.

The **Sozo-iodol** compounds are derivatives of phenol, and present an interesting instance of the changes produced in the physiological properties of drugs by alterations in their chemical structure. Their introduction as iodoform substitutes was due

to want of knowledge of these alterations. Phenol has the formula C_6H_5OH, and is usually represented thus  . It is excreted combined with sulphuric acid,  , a much less toxic body, and it has been found that the introduction of the sulphonic acid group, as it is called, with the ring itself, has a similar effect: $SO_2OH.C_6H_4OH$. With the drop in toxicity there is also a drop in antiseptic power, which, however, may be somewhat increased by the introduction of two iodine atoms into the ring, forming sozo-iodolic acid :—



The iodine, however, is not broken off by the body fluids, and the alkaline salts (sozo-iodates), which have been advertised as antiseptics, have no action at all until dissociation takes place. The zinc and mercury salts are of some antiseptic value, owing to the metallic ion, but of course are no better than other metallic salts of simpler construction.

Picrol is the potassium salt of a similar compound derived from resorcin instead of phenol, and is without colour, odour, toxicity, or pharmacological value.

Nosophen is a compound of iodine and phenolphthalein, a body well known as a sensitive laboratory reagent, and recently introduced into medicine as an aperient under various names (purgen, etc.). It is

insoluble in water, slightly soluble in alcohol, and contains 60 per cent iodine.

Antiosin is a soluble sodium salt which is intended for use as an external antiseptic in 2 per cent solution. It is in the form of blue crystals, which have to be carefully protected from the carbonic acid of the air, and from light.

II.—SUBSTITUTES FOR THE ALKALINE IODIDES.

Some of the iodoform substitutes already mentioned have also been given internally. Thus iodol has been given in doses of ·1 to ·5 gm. (1½ to 8 grains): it has been found that half its iodine appears in the urine, showing that it is decomposed in the system. The sozo-iodolate of mercury has been employed in syphilis; but as the iodine is not split off in the body, any effect it may have must be solely due to the mercury. In these circumstances the ordinary perchloride would be equally effective and much cheaper.

A bismuth compound of nosophen which has been named **Eudoxin** has been given as an intestinal antiseptic. It is a reddish-brown, tasteless, and insoluble powder, the dose being ·3 to ·5 gm. (5 to 8 grains) or, for children, ·1 to ·2 gm. (1½ to 3 grains). It has no special advantage over other bismuth compounds, and is, moreover, expensive.

The remaining iodine preparations may be classified according to the substance with which the iodine is combined.

1. *Protein.*—There are a very large number of bodies in which the iodine is more or less closely combined with some form of protein. **Iodalbacid** is a yellowish-white powder, soluble in water, and containing 10 per cent of iodine combined with the albuminous molecule. It is given in tablets of ·5 gm. (8 grains). Though supposed to be tasteless, it is said to develop an unpleasant taste somewhat frequently.* It contains but little iodine, and is expensive. **Iodalbin** contains 21·5 per cent iodine, and is a reddish powder insoluble in water and acids, but soluble in alkalies; it is thus only absorbed from the small intestine. The dose is ·3 to ·6 gm. (5 to 10 grains) in powder or tablets after food. Larger doses may be given. **Iodan** is a 25 per cent solution of iodine in goose-grease,† and is said to be easily absorbed. **Iodoglidine** is a preparation from vegetable albumin with 10 per cent iodine. It is not absorbed from the stomach, and excretion consequently is deferred some twenty-four hours later than when alkaline iodides are administered.‡ It is sold in tablets each containing ·05 gm. (gr. $\frac{3}{4}$) of iodine. This is approximately the amount in 1 grain of potassium iodide. **Iodomaisin** is prepared from iodine and the protein contained in gluten derived from maize. It is a yellowish, bitter, soluble, hygroscopic substance, and the dose is ·1 to ·12 gm. (1$\frac{1}{2}$ to 2 grains) daily.§

---

* Lipowski, *Neuere Arzneimittel*, p. 28.
† *Pharm. Zeitung*, q. Riedel, s.v.
‡ Boruttau, *Deut. med. Woch.*, No. 37, 1907.
§ *Lancet*, Apr. 28, 1906.

Iodosin contains 15 per cent iodine. **Iodoserum** is said to be formed by the action of iodine on blood-serum, and is intended for intravenous or subcutaneous use. **Iodalose** and **Iodogenol** are combinations with peptone, **Iodalia** one with sugar and tannin. None of these substances appear to present any special advantages.

2. *Saturated Oils.*—**Iodipalin** is made with 10, 20, and 30 per cent iodine. It is intended to be given mixed with mucilage by the mouth, or in doses of 5 to 10 cc. (85 to 170 minims) of the 10 per cent solution subcutaneously.

Iodipin, probably the best known of these preparations, is an addition product of iodine and sesame oil, and is made in two strengths, containing 10 and 25 per cent of the element. One gm. (15 grains) of iodide of potassium corresponds to 7·65 gm. (120 grains) of the 10 per cent solution, and 3 gms. (50 grains) of the 25 per cent solution. The dose is 2 to 3 teaspoonfuls of the 10 per cent solution by the mouth; the oily taste may be more or less imperfectly concealed by peppermint or coffee. The 25 per cent solution is intended for inunction. Subcutaneously, the dose is 10 to 20 cc. (ℿ150 to 350) of the 10 per cent solution, or the 25 per cent solution may be used injected *warm* in doses of 2 to 6 cc. (ℿ30 to 90). The injections are somewhat painful, and should be made with a large needle into the gluteal fat. Care must be taken not to introduce the oil into a blood-vessel. The

preparation is efficient, but decidedly expensive. Its main characteristic is that the iodine remains for a long time at the site of injection, is only slowly absorbed, and excreted in small quantities every day. If preferred, iodipin can be given by the mouth, but then, owing to its unpleasant taste, sugar-coated tablets should be prescribed. They contain ·5 gm. (8 grains) each, which is the equivalent of ·05 gm. iodine or ·065 gm. (1 grain) potassium iodide. Two to four may be given daily, not necessarily after food.*

Olivenol Iodate is a combination with olive oil, containing 7·6 per cent iodine. It is intended for subcutaneous administration, in doses of 2 to 10 cc. (ℳ35 to 170), and gives rise to no pain by this method, but may also be given by the mouth if the patient can take the requisite amount of oil without nausea.† The iodine is slowly eliminated, and iodism does not result.

3. *Other combinations.*—**Iothion** is a combination with propane, and is a syrupy fluid containing 80 per cent iodine. It is soluble in glycerin, oils, alcohol, and vaseline, and is intended for absorption through the skin. In a few days 50 per cent of the iodine is said to be absorbed in this way.

Sajodin is a white soapy powder, quite insoluble in the usual media, and containing 26 per cent iodine

---

* Weissmann, *Wien. klin. Rundsch.*, No. 33, 1908.

† Mirano, *Gazz. degli Osped.*, Mar. 10, 1907.

and 4·1 per cent calcium. It is a compound of calcium, iodine, and an organic acid (behenic acid). It is said not to cause iodism. The dose is ·5 gm. (8 grains) in the original tablets. The amount of iodine is one-third less than that in potassium iodide, and in syphilitic cases 3 to 5 gm. (45 to 75 grains) should be given in twenty-four hours.*

Iodival is analogous in its chemical composition to bromural; that is to say, it is a compound of valerianic acid and urea containing one atom of the halogen element in place of a hydrogen. It contains 47 per cent iodine, and is given in tablets, each of which contains ·3 gm. (5 grains) and is the equivalent of 1 gm. (15 grains) potassium iodide. The tablets should be stirred up with a little water before being taken. It is not decomposed in the stomach, but the absorption from the alkaline intestinal contents is said to be very complete. It is said also to be stored in the lipoid tissues to a large extent.†

In the large majority of cases, potassium iodide is tolerated in sufficient doses to produce the desired therapeutic effect, but in a certain number it may be advisable to take no risks and therefore to employ one of the newer iodine compounds. These are mainly devised to fulfil two ends: (1) To pass unchanged through the stomach, and thus avoid any disturbance of gastric digestion; and (2) To remain stored in the tissues after absorption, and there slowly

---

* Lublinski, *Ther. Monatsh.*, June, 1906.

† Rothschuh, *Folia Therap.*, III., p. 9., Jan., 1909.

to liberate small quantities of iodine. On these two points depend the relative infrequency and slightness of toxic symptoms. Many of them have a very small iodine content, though in some cases this may be compensated by a very complete absorption from the bowel. Where only small quantities are set free daily, a powerful and rapid effect cannot be expected, so that unless intolerance is well marked, there does not seem to be any reason for adopting a method of administration, the object of which is, in fact, to obtain a minimal dosage. Where, however, this is necessary, injections of some oily preparation such as iodipin will be found satisfactory. Some of the German writers* speak highly of sajodin.

It does not seem necessary to go quite so far as do Ehrenmeyer and Stein,† who roundly state that the organic iodine compounds possess no advantages at all. These authors, in a careful study of the pharmacology of the iodides, point out that their activity is solely due to the liberation of iodine ions, which are a protoplasmic poison, especially prone to attack cells, the resistance of which has been diminished, as for instance the connective-tissue cells in arteriosclerosis. They advise that, during the administration of iodine, organic acids should be excluded as far as possible from the diet, as tending to liberate free iodine in the digestive canal; milk (lactic acid) should also be avoided, and alkaline

---

* Lipowski, *op. cit.*

† *Ther. Monatsh.*, 1909, abstr. in *Hospital*, June 26, 1909, p. 330.

substances exhibited. They believe that there is an advantage in giving a mixture of the iodides, such as was known some fifteen years ago as the mistura tri-iodidi :—

℞ Potassii Iodidi Sodii Iodidi Ammonii Iodidi āā gr. iij	Tinct. Nucis Vomicæ ℥x Sp. Ammoniæ Aromat. Syrupi āā ℥j Aquam ad ℨj

BROMINE.

In place of the alkaline bromides, a number of substances have been introduced corresponding to the iodine compounds already described. Their sphere of usefulness is, however, still more restricted, partly owing to the fact that bromides seldom produce any disturbance beyond the well-known acneiform rash; and secondly, because the main therapeutic indication for bromides is epilepsy, for which full doses of the bromine ion are usually necessary. This cannot be effected when a drug is given from which the bromine is only very slowly disengaged in the body. A certain number of preparations containing bromine are intended for use as hypnotics; these will not be considered here, but in the chapter devoted to that class of drug.

1. *Combinations with Formaldehyde.*— **Bromalin** is brom-ethylate of hexamethylene tetramine (urotropin) and corresponds in chemical composition to iodoformal. It is in the form of soluble, colourless crystals. The dose is 2 to 4 gm. (30 to 60 grains).

2. *Combinations with Protein.*—**Bromalbacid** is a yellowish-white, soluble powder: dose ·5 gm., (8 grains). **Bromeigon,** a light-brown insoluble powder, with a slightly sweet taste (bromine 11 per cent); **Peptobromeigon,** a similar, but soluble body, usually given in 20 per cent watery solution; **Bromosin,** a yellowish-white powder containing 10 per cent bromine; are all combinations of bromine with protein. **Bromocoll** is a gelatin-tannin compound, containing 20 per cent bromine. It is a tasteless, brownish powder, unacted on by the gastric juice, but dissolved in the small intestine. In epilepsy, large doses, up to 30 gm. (1 oz.) are given.

None of these preparations present any real advantages over the alkaline bromides; any tendency to irritate the stomach in the latter can always be met by prescribing a sufficiency of water. The organic combinations are, moreover, naturally much more expensive.

3. *Combinations with Oils.*—**Brominol** is said to be a solution in sesame oil; **Bromolein,** an addition product of bromine and the unsaturated oil of almonds, containing 20 per cent bromine. It is a yellow, tasteless fluid. **Bromipin,** the corresponding substance to iodipin, is made in two strengths, one containing 10 per cent bromine, the dose of which is 4 to 8 or even 32 cc. (1 drachm to 1 ounce) in hot milk, peppermint water, or syrup; the other containing 33·5 per cent bromine, and dispensed in 2-gm.

(30-grain) capsules, and in tablets, each of which corresponds to 1 drachm of the 10 per cent oil.

The oil preparations do not appear to offer any advantages over those in which some protein substance is employed to combine with bromine. They have, moreover, the disadvantage which all oily drugs possess, namely, that many persons are unable to swallow them without nausea.

4. *Combinations with other bodies.*—**Sabromin** is a preparation analogous in composition to sajodin; it is a white, odourless, and tasteless powder. The dose is ·3 to 1·0 gm. (5 to 15 grains) after food, either in the form of a powder or a crushed tablet. The drug should be taken with a draught of water. It appears to have much the same advantages as the other substitutes for alkaline bromides.

SULPHUR.

Two interesting substances containing sulphur will be considered under this heading, not because their action is necessarily due to the sulphur they contain, but merely as a matter of convenience in classification.

I.—ICHTHYOL.

This body, which is of uncertain composition, has been largely used externally in certain forms of dermatitis, and has also been recommended internally for a variety of conditions; but it is probable that its therapeutic scope and value have both been consider-

ably exaggerated. Its main disadvantage is its unpleasant taste and smell, and to obviate this various substitutes have been devised.

Desichthyol is sulpho-icthyolate of ammonia (the ordinary medicinal ichthyol) which has been deprived of its odorous constituents by passing through it superheated steam. It is intended for external application.

Ichthalbin is a combination with protein which is practically insoluble and consequently tasteless. It is a white powder, containing 40 per cent of the original substance, and is given in doses of ·2 to ·5 gm. (3 to 8 grains). It is decomposed in the small intestine.

Ichthoform, a combination with formaldehyde, is a blackish-brown insoluble powder, odourless and tasteless. It is hardly soluble in alkalies, so that its absorption from the intestine is necessarily very slow. The dose is 1 to 2 gm. (15 to 30 grains) for adults, and a quarter of these amounts for children.

These bodies have been mainly used as intestinal antiseptics.

Ferrichthyol and **Ichthargan** are compounds with iron and silver respectively. The former contains 3·5 per cent "organic" iron and 96·5 per cent ichthyol sulphonic acid. It is given in ·1-gm. (1½ grain) tablets in cases of anæmia. The latter is a brown, amorphous powder, easily soluble in water. It contains 30 per cent silver and 15 per cent sulphur. Its main use is as an injection in

gonorrhœa (·02 to ·2 per cent solution). It has not been largely used.

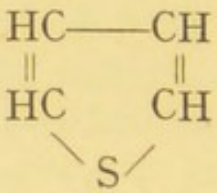
Anytin is a dark brown fluid, obtained from ichthyol, and containing 33 per cent of ichthyol-sulphonic acid. It is combined with phenols (such as creosote, eucalyptol, etc.) to form *Anytols*, which are thought to gain increased antiseptic value in this manner. Though doubtless antiseptics, they do not appear to present any special advantages over other cheaper and better-known substances.

A number of artificial ichthyols have also been prepared. Ichthyol itself is obtained from the tar of a bituminous shale, and contains various sulphur compounds, such as sulphones, mercaptans, and sulphides. **Thiol,** which is manufactured by the action of sulphur and sulphuric acid on certain coal tars, contains mainly sulphones. There is a liquid form, a dark, honey-like substance, forming in water a neutral solution with a slight aromatic smell, like Russia leather. The solid form is a brown powder, the smell of which is similar, and the taste somewhat bitter and astringent. It swells up and then dissolves in water. Thiol contains about 12 per cent sulphur. Externally it may be used as a 10 to 20 per cent ointment in skin affections, or internally in pill form, ·1 gm. (1½ grain) being made up in any suitable basis. **Tumenol** is a similar product, made from mineral oils instead of tar oils, and **Petro-sulphol** another, which closely resembles ichthyol, produced from various kinds of crude petroleum, obtained in the Tyrol. It contains 16·27 per cent

sulphur. **Thigenol,** with 10 per cent organically combined sulphur, is manufactured by a secret process.

These bodies are all less powerful than ichthyol, but they have the advantages of being without odour and of not staining linen. They are all about the same in price, and are mostly much more expensive than ichthyol.

Thiophene is a cyclical body containing one sulphur atom in the ring :—



It is a colourless fluid which may be combined with iodine and bromine to form yellow crystalline substances soluble in alcohol. These bodies, which can be cheaply prepared, are intended to take the place of ichthyol as external applications. They have considerable antiseptic power, and the two derivatives may be employed as dusting powders, or incorporated in gauze for dressings.

The value of these substances depends, of course, on the value to be attached to ichthyol itself. Apart from its employment in dermatology, ichthyol has been given internally in many conditions supposed to result from abnormal intestinal putrefaction. It is only slightly toxic, though its local irritant action has led to its employment as a counter-irritant externally, and may cause diarrhœa when the drug is administered by the mouth. It is absorbed both

by the skin and mucous membrane, and is excreted by the kidneys and intestinal wall, but it seems very doubtful whether it has any pharmacological or therapeutic effects after absorption. It cannot be supposed that any of the numerous substitutes which have been devised are of more value than the parent substance.

II.—THIOSINAMINE.

Before discussing the therapeutic action and value of this body, which was originally introduced into medicine by Hebra in 1892, a few words on its chemical and physical characters, and on those of its chief derivative, will not be out of place.

Urea, as is well known, has the formula $CO\langle^{NH_2}_{NH_2}$ and is called carbamide, the two NH_2 groups being what is known as amide or amine groups. If, in place of the oxygen, an atom of the bivalent element sulphur is substituted, sulpho-carbamide or thio-urea $CS\langle^{NH_2}_{NH_2}$ is formed, a toxic substance causing paralysis of the nerve centres and cardiac failure. Many of its derivatives are also poisonous, and only one has been used in medicine, namely, that in which one of the hydrogen atoms is replaced by the allyl group $CH_2.CH:CH_2$. forming allyl-thio-urea, allyl-sulpho-carbamide, or thiosinamine. This body occurs in the form of shining prisms with a bitter taste, fairly soluble in water, more so in alcohol. It forms acid salts which are decomposed on solution, and has well-marked pharmacological properties. In large

doses it causes depression of the central nervous system, narcosis, and death, with œdema of the lungs and hydrothorax. Smaller doses excite the nervous centres. In therapeutics it was introduced to cause softening and stretching of scar tissue. It was found, however, that it was inactive when given by the mouth, and that hypodermic injections were painful, especially when alcohol was employed in order to obtain complete solution of the drug.

Mendel, therefore, in 1905, suggested the use of a combination of thiosinamine with sodium salicylate, to which the trade name of **Fibrolysin** has been given. This is a white crystalline powder, easily soluble in water, containing one molecule of sodium salicylate to each two molecules of thiosinamine. The 15 per cent aqueous solution is quite unirritating when injected, but unfortunately is unstable; therefore, unless the solution can be freshly prepared each time it is required, the drug must be obtained in sterilized glass ampullæ or bulbs. Each contains ·2 gm. (3 grains) of thiosinamine, which is an average dose. In prescribing a solution of thiosinamine sodium salicylate, all that need be done is to remember that this substance will contain two-thirds its bulk of the active drug, and that the dose must therefore be correspondingly increased. For example, ·2 gm. (3 grains) of thiosinamine will be contained in ·2 × $\frac{3}{2}$ or ·3 gm. (5 grains) of thiosinamine sodium salicylate. This may be dissolved in 2·3 cc. (40 minims) of distilled sterilized water.

Charteris, who has tried thiosinamine in various

conditions, has been uniformly unsuccessful in obtaining any good results. In some cases, however, the drug was given by the mouth or by inunction. In a case of ankylosis of joints, injections of fibrolysin were made daily for three weeks without result, though combined with massage and the iodine ion. In a second similar case the time during which the injections were given is not stated. It was equally unsuccessful. Experiments on animals did not show any chemotactic influence, while of numerous leucocyte counts in the human subject, in only one was any considerable leucocytosis shown to occur after thiosinamine.*

The way in which thiosinamine acts is not clearly understood. It is stated to be a lymphagogue, to increase the passive hyperæmia of the tissues, and to stimulate chemotaxis.† In animals it has been shown to produce a leucocytosis.‡ In two classes of cases, where the results can be clearly demonstrated, it has appeared to do good, namely cases of Dupuytren's contraction, and those of cicatricial contractions following burns, a very large number of which have already been reported.§ It has also been successfully employed in urethral and œsophageal strictures, in rheumatoid arthritis of the progressive form accompanied by fibrous ankylosis

---

* *Brit. Med. Jour.*, Aug. 28, 1909, p. 541.

† Schawlow, *Deut. med. Woch.*, 1909, No. 14.

‡ Dominici, *Il Policlin.*, 1907, No. 10.

§ A number of references are given in *Merck's Annual Report* for 1907, vol. xxi.

of the joints, in elephantiasis, in corneal opacities, and in chronic catarrh of the middle ear leading to adhesions in the tympanic cavity. In such cases the results could be more or less accurately observed. In others, the good results reported are more difficult to be certain about, namely, cases of pyloric stenosis, perigastric or general peritonitic adhesions,* and stenosis of the cardiac orifices. It has been tried without appreciable result in cirrhosis of the liver and other fibrotic conditions of the internal organs. Cases of generalized scleroderma, fibrosis of the corpora cavernosa, and scrotal elephantiasis have also been reported as uninfluenced.†

Success with thiosinamine appears to depend upon two points: firstly, the treatment must be continued for a sufficiently long period, and secondly, the softened fibrous tissue must be in a position which admits of efficient mechanical stretching, either by means of instruments such as catheters and splints, or by means of the natural muscular movements of the body. Thus, in cases of Dupuytren's contraction, splints and massage must be used; in strictures of the œsophagus, rectum, or urethra, bougies and catheters must be regularly passed; while in cases where fibrous stenosis of the pylorus is diagnosed, massage of the abdomen and the stretching of the pylorus by the passage of food are relied on to aid the treatment. Success, therefore, could not be

* Successful animal experiments have been reported by Jervino, *Gazz. degli Osped.*, Feb., 1908.

† Define, *Giorn. Internat. d. Sci. Med.*, xxxi., 1909, p. 193.

expected in such a case where the motor power of the stomach was greatly impaired by dilatation or other cause.

In fibrous ankylosis of joints, the possibility of mechanical aid in stretching the softened fibrous tissue is obvious.

A curious use for fibrolysin has been described by Riedel,* who employed it with apparently good results in two cases of obesity. 2·3 cc. (½ dr.) given every other day, reduced the patient's weight by about 2 lb. a week. The treatment was continued for four months, and the reduction in weight, which was accompanied by marked improvement in general health, had remained permanent till the time of writing, two years after its commencement.

In the following table, the number of injections given in successful cases is shown; it will be seen that in the great majority a large number are required, and the reports often note that no improvement could be detected before some 20 injections had been given.

AUTHOR	DISEASE	NO. OF INJECTIONS	REMARKS
Caudwell ..	Dupuytren's contraction	26	℥ 15 thiosinamine in 10 per cent alcoholic solution.
Strong ..	,,	30	1 ampulla fibrolysin 3 times a week.

* *Münch. med. Woch.*, 1909, vol. ii., p. 1429.

AUTHOR	DISEASE	NO. OF INJECTIONS	REMARKS
Teschmacher	Dupuytren's contraction	50	1 injection a day.
,, ..	,,	40	,, ,, ,,
Hirtler ..	Scar tissue from burn	50	1 ampulla fibrolysin every other day.
Planta ..	,,	25	,, ,, ,,
Define ..	Urethral stricture	20 to 40	1 ampulla fibrolysin daily or every other day.
Strong ..	,,	10	1 ampulla fibrolysin twice a week
,, ..	Rectal stricture	14	1 ampulla fibrolysin every other day.
Pollak ..	,,	20 (about)	1 cc. of a 10 per cent solution of thiosinamine in glycerin and water.
,, ..	Œsophageal stricture	24	.5 cc. 10 per cent solution thiosinamine. 6 wks.' treatment.
Weisselberg	,,	39	1 ampulla fibrolysin every 2 or 3 days.
Halasz ..	,,	6	1 cc. 15 per cent alcoholic solution thiosinamine.
Combe ..	Laryngeal stricture	10	1 ampulla fibrolysin.
Strong ..	Chronic rheumatoid arthritis	30	1 ampulla fibrolysin 3 times a week.
Billaud ..	Gonorrhœal arthritis	25	5 cc. 4 per cent solution thiosinamine; for 3 weeks.

AUTHOR	DISEASE	NO. OF INJECTIONS	REMARKS
Caudwell ..	Pyloric stenosis	64	℥ 10 10 per cent alcoholic solution thiosinamine.
Steuart ..	,,	40	1 ampulla fibrolysin daily for 1 month, then at longer intervals.
Hartz ..	,,	23	1 cc. 15 per cent alcoholic solution thiosinamine twice a week.
Emmerich ..	Peritoneal adhesions	30	1 ampulla fibrolysin 2 or 3 times a week, with longer intervals at first.
Lüth ..	Gonorrhœal prostatitis	8	1 ampulla fibrolysin every 4 or 5 days.
Castellani ..	Elephantiasis	1 to 3 months	1 ampulla fibrolysin every day or every other day.
Sagar ..	Tympanic adhesions	12	5–6 drops of a solution of thiosinamine.

There appears to be no difference between the therapeutic action of thiosinamine and that of fibrolysin; the latter is now almost exclusively employed, as more convenient and much less likely to cause local irritation. The injections are best made deeply into the muscles of the gluteal region, and not subcutaneously in the flank or arm. It is

apparently not necessary that they should be made near the site of the lesion. They are usually made every other day; sometimes every day for some weeks, and then, if improvement occurs, at gradually lengthening intervals. Some authors, however, advise that the intervals should be longer at the beginning of the course, so that tolerance may be established in those cases in which any special idiosyncrasy with regard to the drug may happen to exist. Careful asepsis is of course necessary. Intravenous injections are hardly ever given, nor do they appear to present any real advantages.

In a certain number of cases thiosinamine appears to exert no influence at all, and in others the softening of the fibrous tissue is only temporary. Urethral strictures have recurred five or six months after the treatment was discontinued,* and the improvement in Dupuytren's contraction has not always been permanent.

Slight unpleasant symptoms are occasionally reported; an odour of garlick in the breath after the injections is not unusual, and in a few cases headache, sleepiness, malaise, and fever occur.† The taste of the drug has been observed a quarter of an hour after an injection. "Suffocative sensations" during gastric digestion and a sulphurous taste in the mouth have been observed in one case.‡ Very

* Mankiewicz and Lengemann, *Merck's Reports*, 1904, p. 188.

† Mendel, *Berl. Klinik*, Oct., 1907; Brinitzer, *Berl. klin. Woch.*, 1906, No. 4, p. 104.

‡ Billaud, *Sem. Méd.*, Jan. 1, 1908, p. 7.

occasionally, more serious symptoms have occurred. Thus in a man, aged 54, after six injections of one ampulla of fibrolysin during nineteen days, vomiting and fever with a weak pulse and considerable collapse set in; this was followed by two days' anuria.* The severe symptoms lasted about a week. In another case, that of a man aged 69, who was being treated for Dupuytren's contraction; after eighteen injections, which were spread over a period of nearly two months, epistaxis occurred, which was followed by bleeding from the gums, a purpuric eruption, and hæmaturia; these symptoms continued for eight days; but subsequently the heart failed, and he died. He was a chronic glycosuric, had a systolic aortic murmur, and was subject to occasional anginal attacks.†

Thiodine or **Tiodine** is produced by the action of ethyl iodide on thiosinamine, and has the formula $SC\begin{matrix}NH.C_3H_5\\ \diagdown\\ \diagup\\ NH_2\end{matrix} . C_2H_5I$. It consists of long, colourless crystals, soluble in water, and containing 46·5 per cent iodine. It is said to be rapidly absorbed and also rapidly eliminated. Iodine appears in the the urine about a quarter of an hour after an injection, and continues to be present for twenty-four to forty-eight hours. The dose is ·2 to ·4 gm. (3 to 6 grains) in twenty-four hours. In larger doses of ·5 to ·7 gm. (8 to 12 grains) the iodine

* Grosse, *Münch. med. Woch.*, Apr., 1908, p. 910.
† Pritchard, *Lancet*, Aug. 14, 1909.

may produce gastric disturbances. It is claimed for thiodine that it is a suitable and convenient drug for hypodermic injection, for which purpose glass ampullæ are sold containing ·2 gm. (3 grains). This amount may be injected every other day for a month.

The small amount of iodine which can be given by means of this compound, and the facts that it is unstable and has a disagreeable smell, disqualify it for practical medication; while the possibility of giving it hypodermically does not appear to be any great advantage.

CHAPTER II.

ARSENIC :—(I.) The Cacodylates ; (II.) The Arylarsonates. PHOSPHORUS :—(I.) The Glycerophosphates ; (II.) The Nuclein and Lecithin Compounds. BISMUTH :—Preparations for external and for internal use. IRON :—(I.) Preparations for external use ; (II.) Preparations for internal use.

ARSENIC.

THE therapeutic applications of arsenic are so numerous that the appearance of new chemical derivatives by which it may be administered cannot fail to be of considerable importance to practical physicians.

Without entering in detail into the pharmacology of arsenic, it may be noted that its action in the body is not due to the metalloid as such, but to the ion of arsenious acid, in which arsenic acts as a trivalent element ; and that it is generally held that arsenic acid compounds, in which arsenic is quinquevalent, are gradually reduced to arsenious compounds (arsenites) in the tissues. Arsenious anhydride or trioxide is commonly known as arsenic or arsenium in medicine ; its toxicity is much modified by its insolubility, so that the fatal dose varies very much, according as more or less is absorbed or ejected ; ·1 gm. (1½ grain) has been known to cause death.

The accompanying structural formulæ will show the relationship of the two classes of arsenical salts to one another :—

Arsenious oxide or anhydride $\left.\begin{matrix}\\ \end{matrix}\right\}^{III} As_2O_3$ $O=As-O-As=O.$

Arsenious acid H_3AsO_3 $HO-As(-OH)-OH$

Arsenic oxide or anhydride $\left.\begin{matrix}\\ \end{matrix}\right\}^{V.} As_2O_5$ $O=As(=O)-O-As(=O)=O$

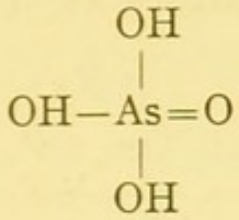
Arsenic acid H_3AsO_4 $HO-As(=O)(-OH)-OH$

Two distinct series of compounds have of recent years been introduced into medicine, whereby it is claimed that large quantities of arsenic can be introduced into the body without producing toxic symptoms, while an increased therapeutic action corresponding to the increased dosage is attained. In order to estimate the validity of these claims, it is necessary to consider first of all the chemical structure of the substances concerned. They are all derivatives of arsenic acid, H_3AsO_4, combined with organic carbon in such a way that they do not give Marsh's test for arsenic until decomposed by the action of powerful oxidizing agents.

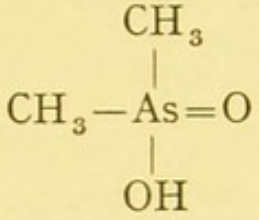
I.—THE CACODYLATES.

As early as 1841 Bunsen* pointed out the relatively non-poisonous character of the body known as cacodylic acid, the structural formula of which, and its relation to arsenic acid is shown thus :—

Arsenic Acid



Cacodylic Acid



Sodium Cacodylate $(CH_3)_2As.O.ONa$ was introduced in 1899 by Gautier, who gave it intravenously in order to avoid imparting the odour of garlic to the breath, which is due to the formation of cacodylic oxide, and invariably occurs when the cacodylates are administered by the mouth or even subcutaneously.† The dose is ·03 to ·06 gm. (½ to 1 grain) hypodermically ; and as commercial specimens contain a variable amount of water as well as traces of cacodylic acid, a standardized preparation should always be used. Arsycodile is the trade name for a number of sodium cacodylate preparations. The iron salt, a yellowish-white powder, is given in rather larger doses, up to 0·1 gm. (1½ grain). A compound with guaiacol, known as cacodyliacol, consists of reddish-white crystals soluble in oil and water. The dose is up to ·13 gm. (2 grains).

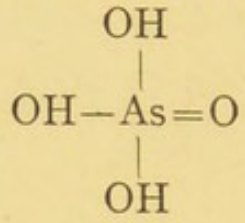
---

* Fortescue-Brickdale, *Guy's Hosp. Reports*, vol. lviii., p. 35, 1904. (References to earlier work.)

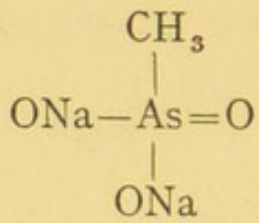
† Fraser, *Lancet*, 1902, vol. i., p. 1902.

A second organic arsenic derivative, also introduced by Gautier, is that containing one methyl group and two atoms of sodium, which he has called **Arrhenal.**

Arsenic Acid



Arrhenal



This body is a colourless, crystalline salt, soluble in water and alcohol, and non-hygroscopic. Its solutions are alkaline. The advantage claimed for it is that it may be given by the mouth, and that no odour of garlic is imparted to the breath. This, however, is not the case, as has been frequently shown.* The dose of arrhenal is ·025 to ·1 gm. daily ($\frac{1}{2}$ to $1\frac{1}{2}$ grains).

After a somewhat extensive trial, these compounds have been found to present no advantages. As has been shown by Sir Thomas Fraser,† very large doses can be given: as much as $11\frac{1}{2}$ grains of sodium cacodylate to a boy of 9 years, and 9 grains of arrhenal to a girl of 13 years, in the 24 hours. The greater part can be recovered unchanged in the urine, and the non-appearance of toxic symptoms is due to the fact that these drugs are only decomposed to a very slight extent in the body; their therapeutic efficacy is also slight for the same reason, and the majority of clinicians no longer employ them.

---

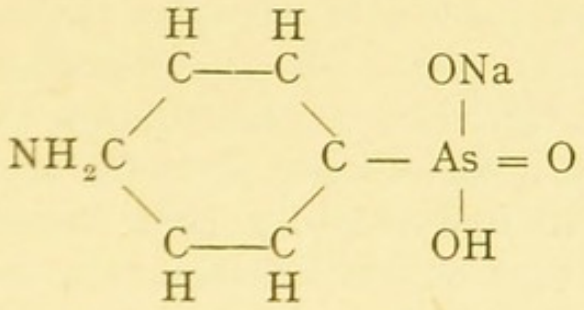
* Hartzell, *Jour. Amer. Med. Assoc.*, 1908, vol. ii., p. 1484.

† *Scot. Med. and Surg. Jour.*, vol. xii., p. 193, 1903.

II.—THE ARYLARSONATES.

The second class of organic arsenic compounds have been more recently introduced, and apparently will attain a much larger measure of usefulness. They are known as the arylarsonates, and have been mainly used in cases of trypanosomiasis and syphilis, though other diseases for which inorganic arsenic is commonly prescribed have also been treated with them.

1. **Atoxyl, Arsamin,** or **Soamin** is chemically the sodium salt of *p*-amidophenyl arsenic acid, or mono-sodium-arsenate combined with *p*-amidophenol $NH_2.C_6H_4.OH$. (sodium *p*-amidophenyl arsonate). It was at first thought that the acid was united to the nitrogen in the amide (NH_2) group, but it has now been shown* that it is attached directly to the ring, and that the structural formula is consequently



Atoxyl is a white, crystalline powder, devoid of taste or smell, and easily soluble in water (1 part in 5 of warm water). It is decomposed in the stomach, and is consequently only given subcutaneously. No local symptoms occur when deep injections are given. In some cases toxic symptoms have occurred, such

* Moore, Nierenstein, and Todd.

as dizziness, vomiting, headache, and fever, followed by temporary or permanent blindness.* It is difficult to form any accurate idea of the frequency of ocular complications occurring after treatment with the arylarsonates; Ernest Lane† has recently called attention to the subject, mentioning four cases of total blindness due to optic atrophy which have come under his notice. Three of these patients had been treated with soamin, and one with orsudan (*vide* p. 52) and a fifth case from the literature is quoted in his paper, also after the use of soamin.

Fehr‡ has published accounts of four cases after atoxyl, two of which recovered. Nonne§ and Herford|| have each published a case. The latter considers the prognosis hopeless.

Among 1,633 cases of sleeping sickness treated by Koch, there were twenty-two cases of blindness, and O. Seifert¶ has notes of twenty other authors, besides those mentioned above who have recorded cases.

There is no evidence at present that optic atrophy is less likely to occur with any particular arylarsonate. The fact that the majority have occurred after atoxyl is accounted for by the much larger trial which this substance has received.

---

* *Brit. Med. Jour.*, 1907, vol. ii., p. 293; *Bull. de l'Acad. de Méd.*, July 9, 1907.

† *Brit. Med. Jour.*, 1910, vol. i., p. 599.

‡ *Deut. med. Woch.*, xxxiii., 49, 1907.

§ *Med. Klin.*, iv., 20, 1908.

|| *Charité Ann.*, xxxii., p. 440, 1908.

¶ *Würtzberger Abhandlungen*, Bd. I, Heft 1, 1900; Bd. V, Heft 1, 1904; Bd. IX, Heft 1 and 2, 1908. *Nebenwirkungen der modernen Arzneimittel.*

Anginal attacks, jaundice, and nephritis have occasionally occurred, besides optic atrophy and retinal hæmorrhages. A fatal case has been recorded in a patient, aged 28, who was being treated for primary syphilis. He had previously been given mercurial inunction and four injections of salicylate of mercury (·1 gm.) subcutaneously. Four days later atoxyl injections were begun, and of these, four were given in one week, to a total of 2·4 gm. (about 37 grains). He died in the course of an epileptiform attack. The other symptoms were cyanosis, vomiting and pyrexia.* The source of the atoxyl is not stated. French writers consider the German products responsible for these untoward results, owing to the presence of impurities (arsenates and arsenites). German observers consider that some patients show a special idiosyncrasy. Both views are conceivably correct, and in any case the initial doses should be small, and considerable care should be exercised in the selection of a brand of guaranteed purity.

Igersheimer and Itami found, as the result of experiments on animals, that severe hæmorrhage into the kidney (dogs) and in subacute cases degenerative changes in the brain and spinal cord (cats) occurred, and that added to these were the ordinary symptoms of inorganic arsenical poisoning. Various other aromatic arsenic derivatives gave similar results to those obtained with atoxyl.†

* Schlecht, *Münch. med. Woch.*, 1901, i., May 11.
† *Archiv. f. exp. Path. und Pharm.*, lxi., p. 18, 1909.

Yakimoff* recommends that, before injecting any solution of atoxyl, a little should be warmed in a test tube; the faintest trace of a yellow coloration should cause the sample to be rejected.

The action of atoxyl is apparently not specific in any of the diseases for which it has been given. In trypanosomiasis a 20 per cent solution in *warm* sterile normal saline is injected subcutaneously or, better, intramuscularly. For four to six days ·6 cc. is given, then for a similar period ·8 cc., and after that 1 cc. This dose is continued till toxic symptoms appear, when the amount is reduced to within the limits of individual toleration.† This treatment, in combination with other remedies (mercury and certain aniline dyes), has been found more satisfactory than any other yet tried, though not invariably successful. There are two theories as to the way in which atoxyl acts in trypanosomiasis. Ehrlich, noting that *in vitro* it did not affect the trypanosomes, supposed that a reduction product, *para*-amidophenyl oxide was produced in the body, and showed experimentally that this substance actually had trypanocidal power. Owing to some experimental difficulties in accepting this view, Levaditi assumed that certain proteins derived from the body cells acted as a link or amboceptor between the organic oxide and the trypanosome. Breinl and Nierenstein,‡ however,

---

* *Deut. med. Woch.*, xxxiii., 41, 1907.

† Todd, *Brit. Med. Jour.*, 1906, i., p. 1037.

‡ *Annals of Tropical Medicine and Parasitology*, III., i., p. 395, 1909 (references to former literature).

have failed to find any evidence of a reduction product in the animal body except to a small extent in the alimentary canal. They believe that an oxidation process occurs in the atoxyl which is retained in the body, enabling it to be excreted in the less toxic form of a sulphuric or glycuronic acid derivative. A small residuum they believe to circulate in the plasma combined by means of its amide (NH_2) group with the proteins. An oxidation process is then set up, destroying the aromatic nucleus and causing *nascent* arsenic to be produced which kills the trypanosomes. The atoxyl circulates mainly in the plasma, and is almost entirely excreted as such in the urine within twenty-four hours.* Long-continued autolysis produces more complete disintegration, inorganic arsenic being split off and giving rise to the well-known toxic symptoms.†

In syphilis, it seems certain that injections of atoxyl cannot take the place of the classical treatment by mercury.‡ In many cases a temporary improvement occurs, but the symptoms soon recrudesce after the injections have ceased. Professor Hallopeau§ considers that the action of atoxyl is valuable, but that enough of the drug cannot be given to entirely destroy the infecting organism without inducing toxic symptoms. Old persons, those of small stature, and those with

* Lockemann and Paucke, *Deut. med. Woch.*, xxxiv, 34, 1908.
† Igersheimer and Rothmann, *Chem. Centralblatt*, 1909, i., No. 19, p. 1595.
‡ Charmeil, *L'Echo méd. du Nord*, 1908.
§ *Brit. Med. Jour.*, 1907, i., p. 1458.

other organic diseases, are predisposed to toxic manifestations, and should be given smaller doses. In about fifteen days no further trace of arsenic can be found in the urine, so that it might be safe to begin a second course of injections after such an interval. Hallopeau quotes certain animal experiments which seem to show the value of atoxyl in syphilis, and also says that in his view it is the arsenic rather than the aniline which is the remedial agent in its composition.

Pernet probably expresses an opinion which is shared by most authorities on the subject when he writes: "It has been proved that atoxyl . . . . and similar or derivative arsenical compounds are of no real avail in the fundamental treatment of syphilis, however useful they may be in clearing up some lesions for the time being, or as adjuvants."*

According to the usual method recommended, a 10 or 20 per cent solution is used, and two injections of ·75 gm. (12 grains) atoxyl are given at two days' interval, then four of ·5 gm. (8 grains) at three days' interval. Others give ·5 gm. (8 grains) for three injections every other day, and 1 gm. (15 grains) on the tenth day.† After fifteen days the mercurial treatment should be begun. In all cases, signs of poisoning—headache, dizziness, fever, nausea, deafness, dry cough without physical signs, retention of urine and strangury, and somnolence, should cause immediate suspension of the treatment. The

* *Folia Therap.*, iv., 2., 1910, p. 41.
† *Lancet*, 1908, ii., p. 1576.

following totals have produced untoward results:* 2·7 gm. (43 grains), 1·8 gm. (29 grains) in eleven injections; 2 gm. (31 grains) in twelve injections; 2·64 gm. (42 grains) in twenty-four injections.

Colonel Lambkin† gives rather larger doses—·648 gm. (10 grains) on alternate days till 6·48 gm. (100 grains) have been given. He considers the remedy of great value, but recommends the subsequent use of mercury in recent infections.

His cases show that atoxyl and its derivative arsacetin are also of considerable value in cases of old-standing syphilitic lesions which have proved refractory to treatment by mercury and iodides.

Although Colonel Lambkin previously agreed with the opinion that atoxyl should not be given while mercury was being prescribed, he has recently somewhat modified his views on this point, and now in early syphilitic infections is accustomed to give injections of a compound known as atoxylate of mercury.‡ It contains 23·7 per cent arsenic and 31·8 per cent mercury, and is a white powder practically insoluble in water. It is given intramuscularly in suspension with olive oil, liquid paraffin, or some suitable creamy vehicle. Colonel Lambkin's scheme for its administration is:—

Hydrarg. Atox. ℥j Vehicle ℥ix

	1st injection,	♏ vij = gr. ¾ (·05 gm.).
After 3 days—	2nd ,,	,, ,, ,,
,, ,, —	3rd ,,	♏ xij = gr. iss (·1 gm.)
,, 7 ,, —	4th ,,	,, ,, ,,

* *Münch. med. Woch.*, 1907, i., p. 937.

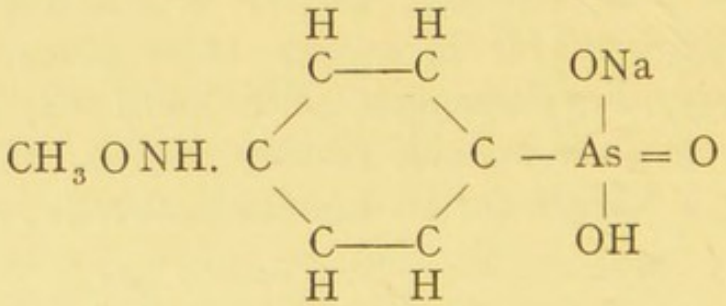
† *Lancet*, 1908, ii., p. 1656. ‡ *Ibid.*, Jan. 1, 1910, p. 23.

and so on till eight injections have been given. After a month's rest, the course is repeated. Cases treated during the six months previous to the publication of the paper are quoted to show the good results of this system.

In certain skin diseases, and in other conditions for which arsenic is given, atoxyl injections may be employed, but it has hardly been shown that they possess any marked advantage except that of bringing the patient somewhat rapidly under the influence of the drug. ·15 to ·3 gm. (2½ to 5 grains) may be given every two or three days in 10 per cent solution; 17 to 20 injections may be required.

Owing to the chemical instability of solutions of atoxyl, they must be made freshly for each injection, and must not be more than slightly warmed before use.

2. **Acetyl Atoxyl** or **Arsacetin** is an atoxyl derivative having the formula



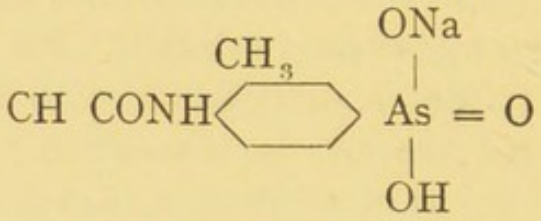
as is implied by its name. It is soluble in water (1 part in 10), and the solutions may be boiled without decomposition, which is the main advantage obtained by the use of this compound.

It is apparently less toxic for certain animals (monkeys, fowls and rats*) than atoxyl, which might be expected from its greater chemical stability, and the fact that the percentage of arsenic is less. It has been successfully employed in sleeping-sickness, in certain skin diseases, and in syphilis. Neisser, who states that 5 gm. of atoxyl are equivalent to 6 gm. of arsacetin, recommends ·6 gm. (10 grains) on two consecutive days each week, in a warm 10 to 15 per cent solution. He gives a large total—14 gm. (half an ounce). Nephritis is a contra-indication for the use of the drug.† Heymann‡ advises a 20 per cent solution, 3 cc. being injected at a time (= ·6 gm. or 10 grains). The solution, syringe and needle must be well warmed to prevent the drug from crystallizing out. In twenty out of thirty-one cases, mainly with secondary symptoms, he obtained good results. In 23·6 per cent the treatment had to be discontinued owing to toxic symptoms. Heymann thinks the action of arsacetin in syphilis appears to be very similar to that of atoxyl; Colonel Lambkin§ gives a total of 4·5 gm. (70 grains), the injections taking place on alternate days; the German writers give as much as 7·2 gm. in all (115 grains). It does not appear that a permanent cure can be expected, though rapid improvement of the symptoms often occurs. Acetyl atoxyl cannot be given with mercury any more than

* Salmon, *C. Rendus l'Acad. des Sciences*, June 22, 1909.
† *Deut. med. Woch.*, Aug., 1908.
‡ *Ibid.*, Dec., 1908. § *Loc. cit.*

can the parent substance, and the same rule for the administration of this drug must be followed.* Optic atrophy has been observed in one case after 3·6 gm. of arsacetin had been injected for psoriasis.†

3. **Orsudan** is an atoxyl derivative which only differs from arsacetin in containing one more methyl group. Its structure is represented by the formula



Doses of ·64 gm. (10 grains) are injected intramuscularly, dissolved in a drachm of distilled water at 100° F. The dose is repeated every other day till 6·4 gm. (100 grains) have been given. The results which have been reported show that this compound closely resembles arsacetin‡ in its therapeutic action in cases of syphilis ; it is, however, obvious that the patients will require much more prolonged observation before any final opinion as to the results can be given.

Arsan or arsenglidin is a preparation with vegetable protein containing about 4 per cent of arsenic. It is fairly easily split up in the organism, and is said to be a useful drug.§

---

* Blumenthal and Jacoby, *Biochem. Zeitschr.*, xxi., 1, p. 20, 1909.
† Rüte, *Münch. med. Woch.*, lvi., 14, 1909, i.
‡ *Clin. Jour.*, 1909, p. 257.
§ Löb, *Med. Klin.*, v., 17, 1909.

PHOSPHORUS.

Phosphorus may be administered to man or animals in its elementary condition, or combined with organic or inorganic radicles; it should, however, be distinctly understood that whereas the first-named is a powerful poison, acting on many cells and profoundly affecting metabolism, the two classes of compounds derived from it are comparatively inert substances, as to the pharmacological action of which there is at present very little direct evidence.

The newer phosphorus compounds have apparently been introduced with a view of supplying the organism, and especially the brain and spinal cord, with the materials for the manufacture of lecithins, a group of bodies occurring in the myelin sheath of nerves and elsewhere, and of nucleins—complex bodies occurring combined as nucleo-proteides in all nuclei. It has never been shown, however, that in any conditions of disease the central nervous system is deficient in phosphorus compounds, so that the further amounts given medicinally are only supplying a purely hypothetical want.*

Moreover, were any extra phosphorus required, it could be much more easily supplied by means of a diet rich in phosphorus, such as yolk of eggs, pancreas, liver, and some forms of meat, which contain a far larger amount than that which can be given in many of the new organic phosphorus

* It has, however, been shown that there is a slight decrease in the amount of lecithin in the brain in cases of general paralysis, though none was found in cases of dementia præcox (Wm. Koch).

preparations. As Hart and also W. Koch* have pointed out, any deficiency in the phosphorus supply to the central nervous system can be made good by abstractions from other parts of the body (e.g., the bones) where its presence is less necessary to the organism. That the bones do actually give up their phosphorus in order that cell nuclei shall not suffer from phosphorus starvation has been shown by observations on fasting men.†

Much controversy has taken place concerning the absorption of the organic and inorganic derivatives, a question which cannot be said to be conclusively decided at present. There is a small amount of evidence that the glycerophosphates are in some instances better absorbed than the ordinary inorganic salts,‡ but in these experiments the form of inorganic phosphorus chosen was calcium phosphate. Now the presence of calcium in the intestinal canal has been shown to hinder phosphorus absorption, owing to the formation of insoluble phosphates,§ so that the comparison is not altogether satisfactory. Experiments on animals by Ferrata and Moruzzi|| seem to show that the organism can construct lecithin from all forms of phosphorus compounds ingested.

It has also been stated that the ingestion of

---

* *Jour. Amer. Med. Sci.*, May 1, 1909.

† Von Noorden, *Metabolism and Practical Medicine*, Tr. Walker Hall, vol. ii., p. 44, 1907.

‡ Tunnicliffe, *Arch. Internat. de Pharm. et de Thérap.*, 1906, vol. xvi., p. 207.

§ Von Noorden, *op. cit.*, vol. iii., p. 1079.

|| *Arch. f. Verdauungs Krankh.*, xiii., 3. p. 223, 1907.

phosphates stimulates nitrogenous metabolism, but on this point also the experimental evidence is conflicting. Although the experiments with glycerophosphates quoted above showed that nitrogenous metabolism was diminished and the amount of nitrogen stored in the body was increased; others,* in which the glycerophosphates were injected subcutaneously, and lecithin given by the mouth, produced a contrary result, namely, increased nitrogen loss, and no increased retention of phosphorus. Thus it is impossible at present to say definitely that the administration of phosphorus in an organic form influences protein metabolism one way or the other, but it seems probable that if the diet is rich in phosphorus the exhibition of drugs containing that element, either in organic or inorganic form, will produce no very marked effect.†

I.—THE GLYCEROPHOSPHATES.

The **Glycerophosphates** of calcium, sodium, and potassium were originally introduced because it is in the form of a glycerophosphate that phosphorus occurs in the lecithins. They are, when dissolved, somewhat unstable bodies, and the solutions should therefore always be freshly prepared. The sodium and potassium glycerophosphates are thick, syrupy liquids; the dose is ·25 to ·65 gm. (4 to 10 grains) in water or syrup. ·2 to ·25 gm. (3 to 4 grains) may be injected hypodermically, diluted with

* Marfori, *Archivio di Fisiologia*, fasc. ii., vol. v. 1908.
† Clerc and Cook, *Jour. Biol. Chem.*, 1906, v., p. 251.

normal saline solution. The calcium, iron, lithium, magnesium, and manganese salts are solids soluble in water, the dose being ·2 to ·65 gm. (3 to 10 grains). There is also a quinine glycerophosphate, which is intended as a substitute for ordinary quinine salts, but its advantages are not apparent. The dose is ·1 to ·3 gm. (1½ to 5 grains).

Tonols are a trade name for Schering's glycerophosphates.* The glycerophosphates are frequently prescribed in the form of a syrup, which is sold ready made by many manufacturing chemists. They do not keep well.

Sanatogen is a compound of calcium glycerophosphate with casein from cows' milk—the latter being a phosphorus-containing protein. It is given in doses of 40 to 50 gm. (10 to 12 drachms) a day. It is said to stimulate nitrogenous absorption,† besides being an effectual method of giving inorganic phosphorus.

II.—THE NUCLEINS AND LECITHINS.

Nucleol is a preparation of nuclein prepared from yeast. There is a solution (5 per cent) the dose of which is ·6 to 3·5 cc. (10 to 60 minims); a **Liquor Nuclei** is also prepared, the dose of which is 7 cc. (2 drachms), and tablets containing ·065 gm. (1 grain).

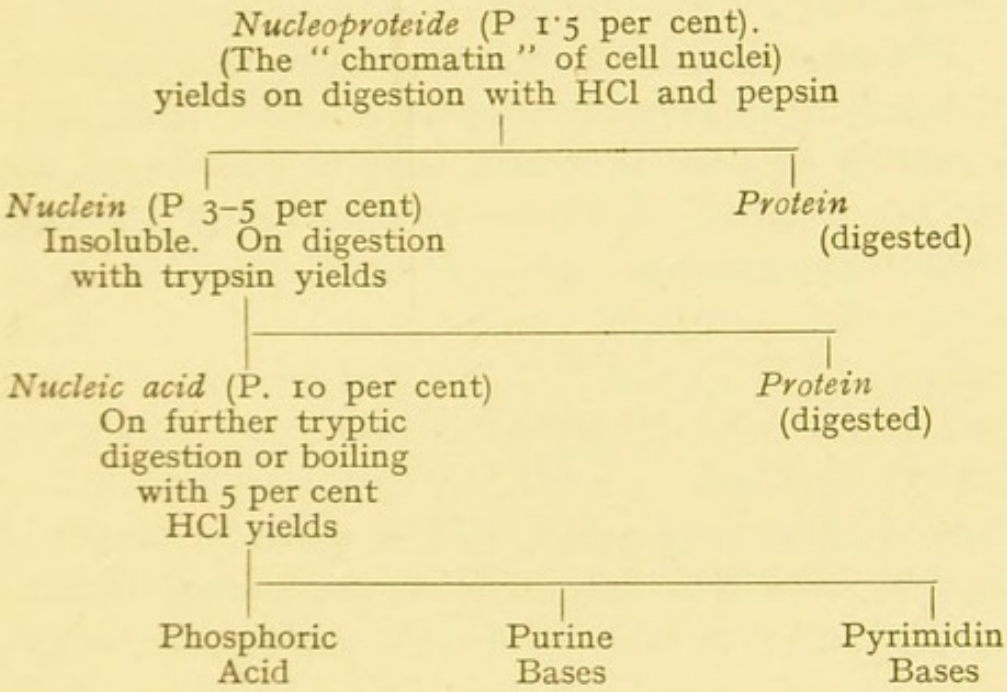
Nucleinic or **Nucleic Acid** is a greyish-white powder, only slightly soluble in water and dilute acids, but easily in dilute alkalies. The dose as a

---

* *New and Non-official Remedies*, 1909, p. 68.

† *Vide supra.*

powder (or in pills or tablets) is ·06 to ·3 gm. (1 to 5 grains), or as a 5 per cent solution (sodium salt) 3·5 to 7 cc. (1 to 2 drachms). Hypodermically 1 cc. (15 minims) may be given. The relationship of these bodies to one another will be seen by the following table :—

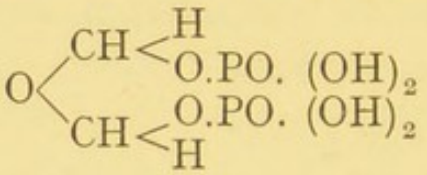


There seems no special therapeutic advantage in these bodies over the ordinary beer yeast, which was official in the B.P. (1885). Their main pharmacological effect is to produce a marked leucocytosis.

Protylin is a compound of phosphoric anhydride (P_2O_5) with protein. It is said to contain 2 per cent of phosphorus and 80 per cent albumin, and is a yellowish-white powder, almost tasteless and odourless, completely insoluble in cold water and very nearly so in hot. It is easily soluble in alkalies, and precipitated from its solutions by dilute acids, and

is thus only dissolved in the body when it reaches the intestine. Enormous doses may be given without producing toxic effects.* The ordinary dose is 2 to 4 teaspoonfuls added to food; children may be given 1 to 3 teaspoonfuls. Combinations with bromine and iron are also on the market (bromprotylin, ferriprotylin).

Phytin.—This is an organic phosphorus compound isolated by Posternak in 1903† from the seeds and rhizomes of various plants, said to contain 22 to 26 per cent of the element. Chemically it is anhydro-oxymethylene-diphosphoric acid :—



The calcium magnesium salt is a white, tasteless powder, sold in gelatin capsules, containing ·15 gm. (2·4 grains); a tablet preparation with milk sugar is also made for children and called *fortassan*.

Mangolan is an organic phosphorus compound which has been used in diabetes.‡ It is calcium anhydro-oxydiamine-phosphate.

BISMUTH.

The newer preparations of bismuth are intended for use in two ways: (1) As external preparations similar to iodoform; (2) As internal preparations

* Gallanga, *Il Policlin.*, Mar., 1906.
† *C. Rendus Soc. de Biol.*, 1903, t. lv., p. 1190.
‡ Nachmann, *Aerztl. Rundschau*, 18, 1906.

having an antiseptic and somewhat astringent action on the intestinal mucous membrane. In both these categories the bismuth plays mainly a mechanical part, as it ensures a finely divided, soft, voluminous powder. The compounds may be divided into three classes, namely (*a*) those containing protein, (*b*) those containing an organic acid, and (*c*) those containing a phenol derivative.

(*a*). **Bismutose** is an albuminate of bismuth containing 22 per cent of the metal and 66 per cent protein. It is a white powder, without taste or odour, turning light grey on keeping. It is insoluble, and passes unchanged through the stomach. The dose for infants is 1 to 2 gm. (15 to 30 grains). Older children can take more. It may be given mixed with rice jelly or added to albumen-water, broth, or tea. 10 per cent to 20 per cent solutions may be used as enemata or for stomach-washing. It may also be applied externally as a dusting powder.

Bismuth Peptonate has also been prepared, also a body called **Parabismuth,** a yellowish powder said to be mainly composed of paranucleinate of bismuth.

(*b*). A large number of organic acids have been combined with bismuth; with regard to their use as dusting powders, all these compounds are of similar value, as the precise form of the organic acid does not affect the physical character of the preparation, and it is upon this that its usefulness depends.

Internally, these substances pass unchanged through the stomach, and are split up in the alkaline intestinal juice, and here the nature of the acid radicle may be of importance. No antiseptic value as regards the intestinal contents can, however, be ascribed to any of them, as the acid is immediately converted into an alkaline salt, and, as is well known, the alkaline salts of the organic acids have no antiseptic action, though largely dissociated in a watery solution.

Besides the well-known salicylate, a dithiosalicylate (or sulphosalicylate) has been prepared and named **Thioform.** It is a yellowish-brown, voluminous, insoluble powder, containing 72 per cent of bismuth oxide. The dose is ·3 gm. (5 grains) several times a day. Externally it may be used as a dusting powder or as a 10 to 20 per cent ointment.

Bismutol is apparently a double compound, and consists of the so-called soluble bismuth phosphate and sodium salicylate. It is used as a dusting powder mixed with talc (1 in 5), in a 1 to 4 per cent solution, or in a 10 to 20 per cent ointment as an antiseptic dressing.

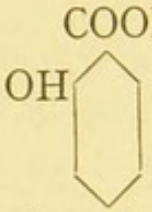
Bismuth Agaricinate and **Subagaricinate** are white powders, practically insoluble in water, and intended as intestinal disinfectants and for use in the night sweats of phthisis. The dose is ·25 to 1 gm. (4 to 15 grains).

The most important compounds, however, of this class are those in which gallic acid is employed. This acid is tri-oxy-benzoic acid, its relation to phenol

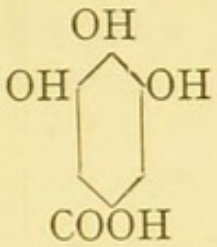
and benzoic acid being shown by the following formulæ :—

Phenol

Benzoic Acid



Oxybenzoic Acid
or Salicylic Acid



Trioxybenzoic Acid or
Gallic Acid

Bismuth subgallate or **Dermatol,** is a yellow, tasteless, and insoluble powder which is frequently employed as a substitute for iodoform. It is well suited for an external application, being non-toxic, non-irritant, stable, and capable of sterilization by heat. Its physical characters are its chief positive recommendation.

Bismal is the methylene digallic acid compound ; it is a voluminous, greyish-blue powder, soluble in alkalies. The dose is ·1 to ·3 gm. (1½ to 5 grains), three to six times a day.

Airol or **Airoform** is the basic gallate of bismuth-oxyiodide, a grey-green, tasteless, and odourless powder, more toxic than dermatol, much less toxic than iodoform. It has no special advantage over dermatol, except that it liberates iodine when

in contact with wounds. It is somewhat unstable, and must be protected from moisture. It may be used pure, or as a 10 per cent suspension in glycerin and water, or as a 10 to 20 per cent ointment.

Crurin is bismuth quinoline rhodonate. It has the disadvantage of producing pain when used as a local application.

(*c*). The phenol derivatives of bismuth differ from those combined with organic acids in being capable of exerting an antiseptic action in the alkaline medium of the small intestine.

Xeroform is tribrom-phenol bismuth, a yellow, non-toxic and non-irritant powder, which may be employed internally in doses of ·5 to 3 gm. (8 to 45 grains). It is insoluble in water, and contains about 60 per cent bismuth. Externally it may be used as a dusting powder, or as a 10 to 20 per cent ointment. The presence of the three bromine atoms in the phenol ring increases its antiseptic action in accordance with a well-established rule.

Orphol is β-naphthol bismuth, a brownish, tasteless, and odourless powder, insoluble in water and alcohol. The dose is ·25 to ·5 gm. (4 to 8 grains) several times daily. Somewhat less is given to children.

Bismutan is a mixture of bismuth, resorcin, and tannin. It is a yellow powder, insoluble in water, with a slightly sweet taste. The dose for adults is ·5 to 1 gm. (8 to 15 grains) during twenty-four hours.

IRON.

I.—PREPARATIONS FOR EXTERNAL USE.

The perchloride and other per salts of iron have long been employed externally as styptics. Recently several preparations have been introduced which are intended to answer the same purpose. **Ferro-** or **Ferripyrin** is a compound of iron perchloride and antipyrin, containing 12 per cent of the former and 64 per cent of the latter. It occurs as dark, orange-red crystals, soluble in water, and may be used in 20 per cent solution; it may also be given internally like the perchloride, the dose being ·05 gm. ($\frac{3}{4}$ grain).

Ferrostyptin is apparently a combination of iron with hexamethylene-tetramine (urotropin)—at any rate, it gives rise to formaldehyde on decomposition with acids. It is a yellow, crystalline powder, soluble in water, and is used in 10 to 40 per cent solution. A compound of **Perchloride of Iron and Quinine** has also been prepared.

There is no reason to suppose that any of these bodies present any advantage over solutions of the perchloride, when used externally.

II.—PREPARATIONS FOR INTERNAL USE.

These are usually divided into two classes, the organic and the inorganic, but the terms are not by any means satisfactory, because they do not in this connection carry their ordinary chemical significance. A better term for "organic" is "larval" or "masked" iron; the only objection to this

being that no corresponding term for "inorganic" iron has been suggested. The most typical inorganic iron preparations are the ordinary salts, such as the perchloride, which give an immediate black precipitate with ammonium sulphide, and a blue colour with ferro or ferricyanide of potassium. The most delicate test is that of Macallum, which is largely used microscopically. It consists in adding to the iron solution some freshly prepared hæmatoxylin (·5 per cent in water), which produces a blue-black colour. The acetate and albuminate of iron are classed as "inorganic," whereas hæmoglobin and some other bodies give none of these reactions, and are termed "organic" or "larval." There are also intermediate substances which after some time give a precipitate with ammonium sulphide.

It is unnecessary here to enter into the prolonged discussions which have taken place as to the absorption and assimilation of the various iron preparations. Briefly, it may be said that two views have been held; one set of observers consider that whereas organic iron can be directly utilized in the manufacture of hæmoglobin, inorganic iron acts only as a stimulant to the blood-forming organs; while others think that all forms are converted into an ionized condition in the intestine. Schirokauer,* who has recently made a number of observations on dogs with gastric fistulæ, and also on the human subject,

* *Zeitschr. f. klin. Med.*, 1909; *vide* also *Med. Chron.*, Nov., 1909, p. 108.

has come to the conclusion that all forms of iron are to a certain extent ionized in the stomach, the protein portion of the organic compounds being at the same time converted into a soluble peptone; the iron is split off and absorbed in loose combination with peptone. This prevents the formation of an oxyhydrate of iron, which is an insoluble and unabsorbable body. All forms of iron undergo the same process, so that the only point which need be considered is the idiosyncrasy of the individual stomach.

Thus, though inorganic iron salts are absorbed and utilized by the organism, just as are the organic combinations, there are certain disadvantages in the former, and perhaps some advantages peculiar to the latter. The more astringent forms of iron are unpleasant to taste, tend to blacken the teeth,* and may set up gastro-intestinal disturbances, with colicky pain, constipation, and secondary nervous symptoms.

Cloetta† found experimentally that ferratin and the tartrate of iron gave precisely similar results as regards hæmoglobin formation, but that the amount

* With regard to the action of iron preparations on the teeth, the following table is slightly modified from one given by Morgenstern (*Therap. Monatshefte*, xxi., 3, 1907):—(1) *Not Injurious*:—Ferratin, F. Reductum, Liq. Ferri Albuminati, Liq. Ferri Manganici Saccharatus. (2) *Hardly at all Injurious*:—Ferri Citras. (3) *Doubtful*:—Tinct. Ferri Pomata, Ferri Pyrophosphas, Ferri Lactas, Ferri Sulphas. (4) *Very Injurious*:—Ferri Iodidum, Ferri Perchloridum.

† Von Noorden, *Metabolism and Practical Medicine*, Trans. Walker Hall, 1907, vol. i., p. 78.

of iron stored in the liver was more than double in the case of the former drug. In young animals, however, ordinary iron-containing food gave better results, as regards hæmoglobin formation, than either inorganic or larval iron preparations, when added to an iron-free diet.

In a large number of cases of chlorosis, one of the less astringent inorganic iron salts administered by the mouth will be found quite satisfactory. Sir T. Clifford Allbutt* recommends the malate, which is a thick, greenish-black extract, forming a clear solution when mixed with water. The dose is ·2 to ·6 gm. (3 to 10 grains). It is made by extracting sour apples with iron wire. The **Tinctura Pomi Ferrata** is composed of one part of the extract dissolved in one part alcohol and eight parts of cinnamon water. The dose is 30 to 90 minims. It is official in many Continental pharmacopœias.†

Perhaps, for other than purely pharmacological reasons, it may be advisable in some cases to try other less ordinary preparations or methods of administration. Intravenous injections of the soluble preparations have been given, but these have now been practically abandoned, even in Italy, where this method of drugging has been in considerable vogue. The following preparations may, however, be administered hypodermically—dialysed iron, citrate of iron, citrate of iron and sodium, citrate of iron and ammonium, and the combinations

* *System of Medicine*, Ed. Alt., vol. v., p. 721, 1909.
† *Squire's "Companion," s.v.* "Ferrum."

with albumin and peptone.* In animals the symptoms of poisoning by iron and sodium tartrate were found to be vomiting, purging, fall of blood-pressure, coma, and death. The excretion of iron salts may also set up renal irritation. Owing to the possibility of this toxic action in man, the doses should always be small—10 or 12 minims of a solution containing $\frac{1}{4}$ to $\frac{1}{2}$ grain of the metal. Apparently one of the most suitable compounds is a 20 per cent solution of the citrate of iron and manganese, the subcutaneous dose of which is 15 minims. This causes no pain or swelling, provided the solution is quite neutral, and is an effective dose therapeutically. Recently a preparation known as **Ferarin** has been placed on the market—a sterile solution of iron arsenate. The dose is 1 cc. (17 min.) every other day. This represents ·02 gm. ($\frac{1}{3}$ gr.) of the salt. Good results have been reported in the secondary anæmia of phthisical patients by hypodermic injections of the citrate (gr. $\frac{3}{4}$ = ·05 gm.) combined with strychnine and arsenic. Usually twenty were given.† In children the advantages claimed are that it is difficult to get them to take enough iron salts by the mouth, and that their digestion is easily upset. Injections of ·05 gm. ($\frac{3}{4}$ gr.) of the citrate may be given every other day in distilled sterilized water.‡

It is important to note that a platinum needle must always be used when making injections of iron

* *Lancet*, 1906, ii., p. 384.
† Peters, *Med. Rec.*, Oct. 10, 1908.
‡ Morse, *Jour. Amer. Med. Assoc.*, July 10, 1909.

salts, as the steel needles easily become corroded. The injections are usually made deeply into the thick tissues of the back or buttocks.* Chalhoub has recommended the chloropeptonate of iron per rectum.†

Of the organic preparations of iron, the following are the most important :—

Defibrinated, sterilized blood, to which glycerin and alcohol have been added in various proportions, forms a stable substance which may be employed as a drug. **Hommel's Hæmatogen,** which is said to contain 80 parts of hæmoglobin and 20 of glycerin, is perhaps the best-known body of this class. **Hæmatol, Landsberger's Hæmatogen Pralines,** (50 per cent Hb protein) and **Hæminol** are similar preparations. They form dark brown solutions, and are frequently flavoured with some aromatic substance, in order to conceal their nature from the patient. **Sicco,** a brown soluble powder, is said to contain 89·52 per cent protein, ·332 per cent organic iron, 2·6 per cent salts, and ·11 per cent fat. **Hæmoferrogen** is a similar brown powder. A solution of sicco in an equal amount of water is sold as **Hæmatogen-Duplex. Fersan** is a combination of the total iron and phosphorus of the erythrocytes with acid albumin‡. The dose is 2 to 5 gm. (30 to 80 grains). The disadvantages of these preparations are that in some cases there is a noticeable taste of

* Da Costa, *Ther. Gaz.*, 1896.

† *Thèse de Paris*, 1883, q. Hale-White, *Text Book of Pharmacology*.

‡ Foelkel, *Münch. med. Woch.*, xlvii, 44, 1900.

blood, and that in many there is present less than one-third of the total weight of hæmoglobin.* Moreover, according to Koning, 1 gm. hæmatogen contains from 36,000 to 700,000,000 bacteria.

Hæmatopan is prepared in ruby-red lamellæ, easily soluble in water, and contains iron prepared from blood, together with about 40 per cent of malt extract. It may be taken in solid form or dissolved, and has a pleasant taste and smell. It is also sold combined with arsenic, guaiacol, and iodine. **Hæmol** is a dark brown powder, consisting of reduced hæmoglobin (hæmatin), and is prepared by the action of zinc on defibrinated blood. The dose is ·1 to ·5 gm. (2 to 8 grains) at meal times. **Hæmogallol** is a red-brown, tasteless powder, insoluble in water. It consists of hæmatin prepared by the action of pyrogallic acid. The dose is 8 grains. It is said to be contraindicated in diseases of the gall-bladder.

In 1894 Schmiedeberg, as is well known, isolated from the liver a body which he called ferratin. This is an intermediate compound, which slowly blackens on treatment with ammonium sulphide. An artificial **Ferratin** produced from albumen was at first thought to be identical with the naturally occurring substance, and to contain a high percentage of iron (6 per cent). It is more probable that the so-called ferratin is merely a nucleo-protein with a variable percentage of iron (0·52 to 3·59 per cent),†

* Clemm, *Berl. klin. Woch.*, 1907.

† Salkowski, *Zeits. f. Physiol. Chemie*, 84, v., 1909.

and that the artificial product is an albuminate and has no connection with the former substance. Artificial ferratin is mainly converted into inorganic iron in the stomach, but as has been mentioned (*vide supra*), it appears to be well absorbed and to be stored in large quantities in the liver. It is non-irritant and easily tolerated by the stomach. It is a brown, tasteless powder, soluble in water and alkalies ; the dose is 1 gm. to 1·5 gm. (15 to 25 grains) daily, for adults. **Ferratose** is a sweetened solution containing ·3 per cent iron. The dose is 1 to 2 drachms.

Arsenoferratose is a combination of iron and arsenic with a protein. It is in the form of a liquid, and the dose is 1 or 2 drachms three or four times a day. It is said to contain ·3 per cent iron and ·003 per cent arsenic in organic combination. The latter does not give the ordinary tests (Marsh, etc.), and is thus shown to be closely bound up with the organic radicle. The advantage of this combination is not apparent, especially as organic arsenic compounds are often excreted unchanged in the urine. The arsenic in a compound of arsenic, iron, and paranucleinic acid, for instance, has been shown to be excreted almost entirely in organic combination in the urine, whereas of the ordinary inorganic arsenic, only a little more than half is excreted in organic combination.*

Carniferrin is the iron compound of carni-

* Salkowski, *Biochem. Zeits.*, xiii., 5 & 6, 1908.

phosphoric acid obtained from beef extract. It contains about 30 per cent iron, and is a red-brown, tasteless, insoluble powder. The dose is ·5 gm. (8 grains) per diem. Like ferratin, it is an intermediate substance, giving Macallum's test, and being slowly changed by ammonium sulphide.

Triferrin* is a paranucleinate of iron, prepared from casein. It is a powder, insoluble in water, but soluble in alkalies, and contains about 22 per cent of iron and 2·5 per cent of organically combined phosphorus. It is not, of course, dissolved till it reaches the intestine. The dose is ·3 gm. (5 grains) thrice daily in powder, chocolate tablets, or solution (triferrol). Biscuits are also made containing it.

Ovoferrin is a solution containing 5 per cent of a protein-iron compound derived from blood-serum and ferric hydrate. The iron contained in it is thus not derived from animal sources at all, but is artificially combined, forming a body called by the manufacturers vitellin. It has nothing to do with yolk of egg. The solution is reddish-brown in colour, and has a slight aromatic taste. It is incompatible with alkalies, but hardly acted on by dilute acids. ·5 per cent HCl only very slowly liberates the iron. It is not astringent. The dose is 2 to 4 drachms (8 to 16 cc.) three times a day.†

Ferroplasma is an interesting preparation, as it derives its iron from a vegetable source. The

* Salkowski, *Zeits. f. Physiol. Chemie*, 84, v., 1909.

† *New and Non-official Remedies.* Published by American Med. Assoc., 1909.

dried root of the docks, *Rumex obtusifolius* and *R. crispus*, contains ·447 per cent of iron in "organic" combination.* It is a powder with an astringent taste, insoluble in water, sold in capsules containing ·1 gm. The adult dose is 2 to 4 capsules after food; children can take 1 to 2. It is said to be easily absorbed, and not to cause digestive disturbances or constipation when given in moderate doses, but is not recommended when the digestion is already disturbed from other causes.†

Hæmatose is another preparation of iron interesting from the pharmacological point of view. It is a compound of albumin with naphthol green (the iron compound of α-nitro-β-naphthol-β-sodium sulphate). It is entirely insoluble in the stomach, but the iron is split off by the action of the intestinal juice.‡

The organic nucleus is thought to be a "nucleone"—a class of bodies occurring combined with iron, phosphorus, and calcium, in milk and in muscle and other tissues. Phosphocarnic acid is one of the best known nucleones, and was obtained from meat extract by Siegfried, who also isolated a rather different body, lactophosphocarnic acid, from milk. Phosphocarnic acid may be precipitated as an iron combination from muscle extracts, as carniferrin.§

---

* *Lancet*, 1909, ii., pp. 164 and 322.

† Da Gradi, *Gazz. Med. Ital.*, Aug., 1907; Oskar Anton, *Prag. med. Woch.*, xxxiii., 43, 1908.

‡ S. Fraenkel, Arzneimittelsynthese Ed. Alt., p. 615.

§ Hammarsten, *Textbook of Physiol. Chem.*, 1904, 4th Ed., pp. 385 and 444.

CHAPTER III.

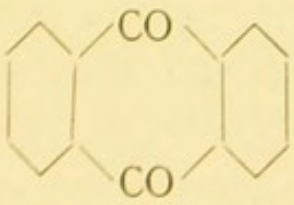
DRUGS ACTING ON THE INTESTINES:—(I.) Purgatives; (II.) Astringents; (III.) Antiseptics. DRUGS ACTING ON THE URINARY SECRETIONS:—(I.) Diuretics; (II.) Antiseptics; (III.) Uric Acid Solvents.

DRUGS ACTING ON THE INTESTINES.

I.—PURGATIVES.

THE vegetable purgatives act, in all probability, directly on the intestinal walls, causing a stimulation which may, if large quantities are administered, go on to the production of actual inflammation. They are, chemically, complex mixtures of various bodies, but such of the active principles as have been obtained in a state of purity appear to be glucosidal in character; that is, they can be split up by dilute acids, or by the means of appropriate enzymes, into a simpler organic substance and a carbohydrate. These bodies, so far as they are at present understood, appear to be derivatives of anthraquinone, a substance closely related to anthracene.

Anthracene.



Anthraquinone.

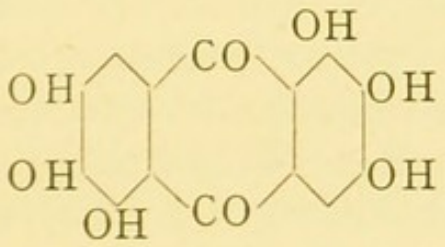
A number of synthetic derivatives corresponding to the natural ones have been prepared, of which two have been introduced into medicine. The activity of these products appears to depend partly on the substitution of the hydrogen atoms in the rings by hydroxyl, and partly on the presence of the CO groups. It is generally considered that the crude drugs act more powerfully than the chemically pure glucosides, and that these again are more active than their decomposition products. The reason appears to lie in the fact that the simpler body is more easily absorbed or decomposed in the intestine, and so ceases to act as a purgative sooner than the more complex glucoside or the crude drug. The main objection to the latter is their bitter taste.

Purgatin or **Purgatol** is a derivative of anthraquinone known chemically as the diacetate of anthrapurpurin (trioxyanthraquinone). It is a yellowish-red powder, insoluble in water, and tasteless. It gives a violet solution in dilute alkalies. It is usually given in doses of ·5 to 1 gm. (8 to 15 grains), but 2 gm. (30 grains) may be required. Tablets of ·25 gm. (4 grains) are prepared, and are a convenient form for its administration. The bowels act in five to twenty hours. As much as 5 gm. (77 grains) have been given without ill-effects. Occasionally slight constipation follows its use. The drug is absorbed, and after about two-and-a-half hours a reddish-brown pigment appears in the urine.* This

* The significance of this curious and interesting pigmentation has recently been studied by A. Krals (Inaug. Diss. Giefsen, 1909,

discoloration reaches a maximum in five hours, and can still be seen in thirty hours after a dose of 2 gm. Marshall,* who experimented on himself, found definite signs of renal irritation after doses of 3 and 4 gm. (45 and 60 grains), with polyuria, lumbar pain, weakness of the legs, and malaise, but no albuminuria. Slight colicky pains occasionally occur. He considers it a mild, somewhat slow, but sure purgative, but not superior to the ordinary crude drugs of vegetable origin. In women the linen is sometimes discoloured by the pigmented urine.

Exodin is a mixture of three of the derivatives of rufigallic acid,† or hexa-oxy-anthraquinone :—



which, in itself, is inactive as a purgative. It is a yellow powder, devoid of taste or odour, insoluble in water and almost insoluble in alcohol. The dose

---

Zeitschr. f. Urologie, Band iii., Heft 9, 1909, p. 779). The occurrence of the pigment was demonstrated by Koberts and Borntræger's tests, and the experiments performed on men and animals. The colour is due to the presence of the oxymethyl anthraquinone group (i.e. to the active principle of the drug) in the urine, and appears to vary directly in intensity with the purgative action. The differences in colour observed with various vegetable drugs and with a preparation of trioxyanthraquinone are noted, and minimal doses producing this effect given in the communication, to which the reader is referred for further details.

* *Scot. Med. & Surg. Jour.*, vol. x., p. 402, 1902.

† F. Zernick, *Apotheker Zeit.*, 1904, No. 63, p. 598.

for adults is 1 to 1·5 gm. (15 to 23 grains), and for children ·5 gm. (8 grains). It is sold as a powder, or in tablets (·5 gm.); the former can be stirred up with water, and swallowed. It is said not to cause colic or any gastric or intestinal discomfort. It acts in eight to twelve hours. Though darkening the colour of the urine, it causes no discoloration of linen.*

Phenolphthalein is known under a large number of trade names, viz., laxans, laxatin, laxatol, laxatolin, laxiconfect, laxoin, laxophen, para-phthalein, phenolax, probilin, purgelin, purgella, purgen, purgo, purgolade, purgylum. It is a phenol derivative, and not at all closely related chemically to the anthraquinone group of purgatives; the only points in common are the presence of a ketonic (CO) group, and of a number of hydroxyls (OH). Phenolphthalein ($C_6H_4CO.O.C(C_6H_4.OH)_2$) is a well-known "indicator," its alcoholic solution being colourless in an acid environment, but bright pink in an alkaline. It was officially used in order to distinguish certain Hungarian wines, which could then be easily identified by the addition of an alkali. They were unexpectedly found to produce diarrhœa in a number of individuals, and by this the purgative properties of phenolphthalein were discovered. Laboratory experiments give varying results according to the kind of animal employed.

Clinically, phenolphthalein is given in doses of ·05 (children) to ·2 gm. ($\frac{3}{4}$ to 3 grains) in powder,

* Ebstein, *Deut. Med. Woch.*, 1904, No. 1, p. 12.

capsules, or tablets. Larger doses up to ·5 gm. (8 grains) are often necessary. It is insoluble in water, tasteless, and odourless. If tablets are employed, they should not be swallowed whole, but powdered or crushed in the mouth. Apparently very little, if any, absorption takes place when medicinal doses are given ; the presence of phenolphthalein is easily demonstrated in the fæces, but neither the drug itself nor any synthetic derivative can be demonstrated in the urine, unless rather large doses are given, when traces appeared unchanged. It has no irritant action on the kidneys, except in large doses (3 to 4 gm.), when a certain amount is absorbed, and contrary to what has been observed with most vegetable purgatives, it does not appear to depend for its effect on the presence of bile in the intestine.* The purgative action depends on its power of producing a solution with high osmotic pressure in the alkaline contents of the small intestine.

The dose is usually given overnight, and the action then occurs after breakfast on the following morning. The same amount (1 to 5 grains) may be given in divided doses after meals, if this is preferred.

Colicky pains and other undesirable symptoms have occasionally been observed, but on the whole, phenolphthalein is a harmless drug. Doses of 2 to 4 gm. (30 to 60 grains) have been taken daily for a fortnight with no bad results. On

* Tunnicliffe, *Brit. Med. Jour.*, Oct. 18, 1902, p. 1224.

the other hand, there is one instance on record where 1 gm. (15 grains) produced toxic symptoms.* This must have been due to some special idiosyncrasy. Gillette† has recorded the case of a child, aged 3, who took twenty-five or more 1-grain tablets. The stomach was washed out one hour and a half afterwards. No symptoms were noted except slight purgation. There is no evidence that it is broken down in the body; Elmer states that, in a series of cases which he investigated, it was found as reliable as most other purgatives, and the efficient dose did not show any great individual variation. Animal experiments seemed to prove that the formation of the soluble sodium phenolphthalein in the small intestine was not the cause of the purgative action.‡ One observer has noted that in cases where piles were present, phenolphthalein aggravated the symptoms due to them,§ though others have not always confirmed this.

On the whole this substance seems to be a pleasant and convenient form of mild purgative, especially useful for children; but in certain cases it fails to act, even in large doses, just as it does in some animals.||

Aperitol is a mixture of the acetate and valerianate

* Best, *Zeitschr. f. Medizinalbeamte*, 1906, No. 12.

† *Jour. Amer. Med. Assoc.*, Nov. 21, 1908, p. 1782.

‡ *Med. Rec.*, vol. 74, p. 838, 1908.

§ Buckley, *Brit. Med. Jour.*, Feb. 11, 1905.

|| For the pharmacology of this and allied substances, *vide* Abel and Rowntree, *Jour. of Pharm. and Exp. Therap.*, Aug., 1909.

of phenolphthalein. The valerian is added as a sedative to avoid griping, which sometimes occurs after purgen. It is a white powder, tasteless, and insoluble in water and dilute acids. It thus passes through the stomach unchanged, but is broken up in the small intestine. The usual adult dose is ·4 gm. (6 grains) in tablets, but as much as double this may be required in the more obstinate cases. Young children may be given ·1 to ·2 gm. (1½ to 3 grains). These doses are said to produce a single action in six to eight hours.

Herschell* has investigated the action of aperitol from the experimental and clinical standpoints. He finds that experimentally ·4 gm. (6 grains) of aperitol increases the peristaltic action of the intestines, but that the effect is not constant even for the same individual; the amount of water in the stools is also definitely increased, but there is no constant ratio between the increase of moisture and the size of the dose administered. He occasionally noted griping, though not often, and in one case an "attack" of piles occurred after a fortnight's use. He concludes that it may be useful as an occasional aperient in patients not habitually constipated, in those who have recently undergone an operation, or as a temporary measure during the course of other treatment; in cases of chronic colitis it may replace the usual dose of castor oil, while as an occasional aperient for children, or where a course

* *Folia Therap.*, iii., 2, 1909, p. 47.

of purgation is indicated (in œdema, ascites, etc.) it is convenient and efficacious; on the other hand it is quite useless in cases of chronic constipation depending on intestinal atony or rectal anæsthesia.

Eulaxans.—This is a combination of phenolphthalein with sodium hydroxide. It is said to be decomposed in the stomach, but it seems more than doubtful if this would give it any particular advantage over the original substance. The dose is ·05 to ·2 gm. ($\frac{3}{4}$ to 3 grains) in a tablet.

Phenol-tetrachlor-phthalein ($C_6Cl_4CO.O.C.(C_6H_4.OH)_2$) has been employed by Rowntree* as a hypodermic purgative. The dose employed was ·4 gm. (6 grains) dissolved in 20 cc. (about $\frac{3}{4}$ ounce) of oil. He states that the effect is mild but prolonged, being laxative rather than purgative, and often lasting from four to six days. It produces no colic and no irritation at the site of injection, and is non-toxic. Its main disadvantages are that it is insoluble in water and only very slightly soluble in oil, and that no stool occurs for eighteen to twenty-four hours. It is difficult, therefore, to see how it could be of any real use in coma, though in extreme gastric irritability and for some cases of insanity it may be of special value.

Many other bodies have been suggested as hypodermic purgatives, but none have been very largely

* *Johns Hopkins Hosp. Bull.*, 1909, ccxxii., p. 293.

tried by the profession. Nicolini* recommends, for instance, 3 cc. (50 min.) of a 10 per cent solution of aloin. He notes that cathartic acid and colocynthin are painful. Dixon† investigated podophyllin, saline purgatives, and various alkaloidal bodies, all of which were unsatisfactory. The only drug which, as a result of his experiments, he was able to recommend was apocodeine hydrochloride, in 1 or 2 per cent solution. This should be neutral, and filtered before use; 2 or 3 cc. (30 to 45 min.) should be given as a dose. There is little or no local irritation, and a result should occur within an hour of the injection.

Regulin is a substance intended for use as a purgative in habitual constipation. It consists of brownish scales, the dose of which is a teaspoonful to a tablespoonful, once daily with food. Tablets are also made, of which three to four may be taken after every meal. It is made of dried agar-agar together with a little watery extract of cascara sagrada. It has the property of absorbing large quantities of water, and so swelling up in the intestine into a soft mass, which, being unabsorbed, irritates the mucosa and provokes peristalsis. Its action is thus practically entirely mechanical. **Para-regulin** is a somewhat similar substance, composed of paraffin and cascara. It is put up in capsules, three of which are to be taken every day. These substances appear to act only in mild cases—in those, in fact, in which

* *Gazz. degli Osped.*, Jan. 19, 1909.

† *Brit. Med. Jour.*, Oct., 18, 1902, p. 1244.

the proper regulation of the diet, with an occasional mild aperient pill, would produce equally good results.

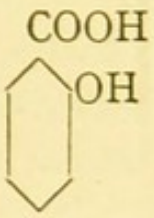
II.—ASTRINGENTS.

Although a large number of cases of diarrhœa, especially in infants, are most properly treated by means of purgatives, which help to remove the cause of the condition, there still remain certain instances in which drugs are indicated which have an astringent action on the mucous membrane. Tannic acid, from its action in precipitating protoplasm and its general astringent action on cells, seems calculated to produce this effect, but it is rendered unsuitable, first by its astringent taste and liability to upset gastric digestion, and secondly by the fact that it is apt to combine with protein material in the food before it reaches the intestinal mucosa. The various modifications, therefore, of tannic acid which have been introduced for use as intestinal astringents, are designed to pass through the stomach unchanged, and to produce no astringent taste in the mouth. They must, of course, be non-toxic and little liable to absorption in the intestine.

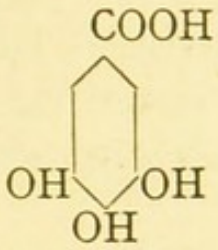
Before considering these bodies in detail, a short account of the chemistry of tannic acid will help to make their constitution and probable value more intelligible.

Tannic Acid or tannin proper is digallic acid, and on hydrolysis yields two molecules of gallic acid with the absorption of one molecule of water. Gallic acid is trioxybenzoic acid, and is thus similar

to salicylic acid in structure, having both hydroxyls (OH) and carboxyl (COOH) attached to a benzene ring. A glance at the following structural formula will make these relationships clear :—



Salicylic Acid
Ortho-oxybenzoic Acid



Gallic Acid
Trioxybenzoic Acid

Gallic acid, then, is $C_6H_2.(OH)_3.COOH$, and two of these, water being eliminated, will form tannic acid :—

$$C_6H_2(OH)_3COO \boxed{HOH} (OH)_2C_6H_2COOH$$

or, $C_6H_2(OH)_3COO.(OH)_2C_6H_2.COOH.$

Besides the true tannic acid, there are a large number of bodies known as "tannins," some of which are glucosides, which yield gallic acid and other substances on hydrolysis, and whose general properties are similar to those of the chemically pure derivative (e.g., kinotannic acid).

Tannigen is diacetyl tannic acid, in which two of the hydroxyl (OH) groups are replaced by acetyl ($CO.CH_3$). It is a yellowish-grey powder, without taste, and smelling slightly of acetic acid. It is insoluble in water and dilute acids, but soluble in alkalies. The maximal dose for adults is 3 to 4 gm.

(45 to 60 grains) daily; children can take ·2 to ·5 gm. (3 to 8 grains) several times a day. At the temperature of the body it forms a sticky mass in the presence of water, and is therefore best prescribed in tablets (5 grains each). In spite of its insolubility, it is astringent in the mouth and stomach. A small quantity passes through the intestine unchanged; some is absorbed and appears in the urine as gallic acid.

Tannoform (methylene ditannate) is a combination of tannic acid and formaldehyde (formol, formalin); it is a pinkish powder, almost insoluble in water but soluble in alkalies. The dose internally is ·25 to 1 gm (4 to 15 grains) several times a day. It is odourless and tasteless. Externally it may be used pure, or mixed with talc or starch (25 per cent to 50 per cent) in hyperidrosis, etc.

Tannopin is a compound of hexamethylenetetramine (urotropin) and tannic acid. It is a fine, fawn-coloured powder, insoluble in water and weak acids, and gradually decomposed by weak alkalies. The dosage is the same as that of tannoform, but does not give rise to so much formic aldehyde as does that body; consequently, it is not such a powerful antiseptic. It is without taste or odour.

Tannothymol is a condensation product with thymol and formaldehyde, and is a yellowish-white or reddish powder, insoluble in water and acids but soluble in alkalies. The dose is 1 gm. (15 grains) several times daily.

Tannal (insoluble) is a basic aluminium tannate.

It is a brown powder, soluble in dilute alkalies. A soluble tartrate of aluminium and tannin is also prepared under the name of **Tannalum Solubile,** intended for use as a gargle or throat application.

Besides these compounds, which are intended also to act as antiseptics, there is a class of derivatives made by acting on various forms of protein with tannic acid, and producing a stable product by long heating or some other means. **Tannalbin** is perhaps the most important of these. It is a brown powder, insoluble in water and acids, but soluble in alkalies; is without taste or smell, and contains 50 per cent tannic acid. The dose is 1 to 4 gm. (15 to 60 grains) in powder or tablets, followed by a draught of water. Infants can take ·3 to ·5 gm. (5 to 8 grains) in gruel, barley-water, or other suitable liquid. **Honthin** is a similar substance used in the same doses. **Tannacol** is a combination with gelatin, and **Tannocase** one with casein. The characters and dosage of all these compounds are the same.

These are all useful substances, and superior to the first group of tannic acid derivatives in that, while completely broken up in the small intestine, they have no astringent or other effect on the mucous membrane of the stomach.

III.—ANTISEPTICS.

Ever since bacteriology began to play a dominant part in theories as to the causation of disease,

attempts have constantly been made to discover a drug capable of efficiently disinfecting the alimentary tract, and especially the small intestine. In all probability the substances recently introduced will not prove more efficacious than the older remedies. Grey powder, blue pill, the various preparations of bismuth, and possibly β-naphthol are, as far as is known, the best substances of this class.

More recently, various tannic acid derivatives (tannoform and tannopin) have been tried. These have already been described (*vide* p. 84). The newer naphthol preparations include the salicylate (**Betol**) and the benzoate. These are white crystalline powders, practically insoluble in cold water, glycerin, or alcohol. They are not acted on in the stomach, but are split up in the small intestine, where the antiseptic action of their components is said to be produced. The dose is ·3 to ·5 gm. (5 to 8 grains) in cachets or suspended, the maximal single dose being 1 gm. (15 grains) and the maximal total for twenty-four hours 4 gm. (60 grains).

Attempts have also been made to bring the antiseptic action of nascent oxygen to bear on the intestinal contents. Two peroxides of organic substances have been introduced for this purpose. **Acetozone** (benzoylacetyl peroxide) is a soluble crystalline substance; it is sold mixed with an insoluble absorbent powder which is physiologically inert. The solution for use is prepared by adding 1 gm. to 1,000 cc. warm water (15 grains to one quart), shaking the mixture vigorously for five

minutes, and then allowing it to stand for two hours. The fluid may then be decanted, leaving the insoluble powder behind, and drunk by the patient. In cases of enteric, an adult patient can take 2 quarts or more in the twenty-four hours.

Alphozone is the peroxide of disuccinyl. It is a soft, crystalline powder, which keeps well if protected from exposure to the air. It is sold in powder or tablets (·065 gm. = 1 grain). The solution for internal use (enteric fever) should be about 1–3,000 (1 tablet in 6 fluid ounces). One in 5,000 is said to kill *Bacillus typhi* in one minute.

Sollman,* in a report to the Council on Pharmacy and Chemistry of the American Medical Association, has detailed a large number of experiments on intestinal antiseptics. With regard to formaldehyde (formol, formalin) derivatives, Sollman classifies them as follows :—

1. Those which liberate formaldehyde in acid, alkaline, or neutral media at ordinary temperatures and at body temperatures :—

Hexamethylene-tetramine (p. 96); Tannopin (p. 84). The reaction occurred most freely in acid, and least freely in alkaline solutions. It was more rapid at the higher temperature.

Citarin (p. 105); Novaspirin (p. 249); Glutol (p. 99).

2. Those which do not liberate formaldehyde even on boiling: Formidin (p. 99); Guaialin; Sodi-formasal; Ur-a-sol.

* *Jour. Amer. Med. Assoc.*, 1908, vol. ii., p. 818.

He places the intestinal antiseptics in the following order of efficiency: (1) Bismuth subnitrate, creosote, novaspirin, ur-a-sol, are the best; (2) Tannoform, iodomuth, are nearly as good; (3) Formidin, salol, guaiacol carbonate, tannopin, glutol, are much inferior; (4) Guaialin is practically inactive.

Lentin, which is the trade name for the hydrochloride of *meta*-phenylene-diamine, $C_6H_4.(NH_2)_2$, is, like phenolphthalein, a reagent which has long been employed in the laboratory. In 1893 it was suggested that it might be of value in Asiatic cholera,* and though no clinical trials in this direction were made, subsequent experience showed that it had some action as an intestinal antiseptic in checking diarrhœa of fermentative origin.

Meta-phenylene-diamine hydrochloride is a crystalline powder, soluble in water and alcohol; it is a toxic substance; 1 gm. is sufficient to kill a rabbit, death taking place with general convulsions. No albumin, blood, or sugar have ever been observed in the urine during the administration of the drug; but a peculiar dark-brown pigment is found, which is not hæmoglobin or any blood derivative, but is a product of the drug itself.† Observers have stated that the intensity of this pigmentation is proportionate to the antiseptic activity exerted by the drug in the small intestine,‡ and Duhem says that he has only observed it in cases of tuberculous enteritis, in

* Boye, *Zentralbl. f. innere Med.*, 1905, No. 4.

† Duhem, *Thèse de Lille*, 1906.

‡ Cf. p. 74, footnote.

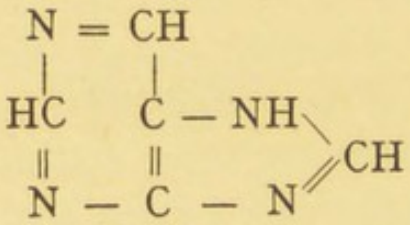
which he found lentin a particularly valuable remedy. The dose is ·01 gm. ($\frac{1}{6}$ grain) once or several times daily for infants and small children ; ·1 gm. ($1\frac{1}{2}$ grain) for adults, with intermediate doses for older children. Duhem gives rather larger doses: for adults ·3 to ·5 gm. (5 to 8 grains), and for children from one to ten years, as many centigrams as there are years in the child's age. Roughly, this would correspond to the following doses : 1 year, gr. $\frac{1}{6}$; 2 years, gr. $\frac{1}{3}$; 3 years, gr. $\frac{1}{2}$; 4 years, gr. $\frac{2}{3}$; 5 to 7 years, gr. 1 ; 8 years, gr. $1\frac{1}{3}$; 9 years, gr. $1\frac{1}{2}$; 10 years, gr. $1\frac{2}{3}$; 12 years, gr. 2. Duhem gives it in the form of pills ($1\frac{1}{2}$ grains) for adults, and in a mixture of mucilage and syrup of orange for children.

DRUGS ACTING ON THE URINARY SECRETIONS.

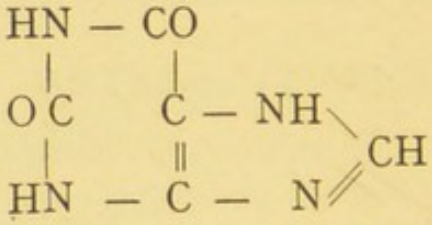
I.—DIURETICS.

The modern series of diuretic drugs are mainly derivatives of the " purines," a class of bodies which have attained a sinister pathological reputation in connection with the mysterious manifestations of gout, the best known of them in this connection being trioxypurine, or uric acid. It may at once be stated that this substance has no diuretic action, and that the recently introduced drugs are all derivatives of dioxypurine, or xanthine, which, in itself inert, first becomes physiologically active by the introduction of methyl (CH_3) groups. If two such methyl groups are introduced, dimethylxanthine is

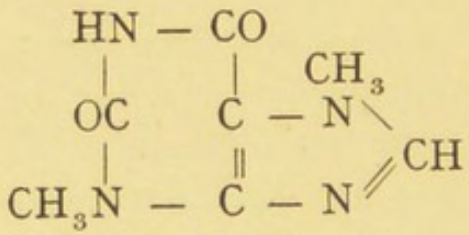
produced, which is capable of existing in two modifications according to the relative positions of the entering groups in the molecule. These two are known as theobromine and theophylline, the latter being also often called by its trade name, theocine. One other important derivative may also be mentioned in this connection, though its diuretic action is not so powerful as that of the previously mentioned derivatives. This substance is trimethyl-xanthine or caffeine, the main physiological effects of which are seen in its action on the central nervous system and heart. The following structural formulæ illustrate the relationship between these bodies :—



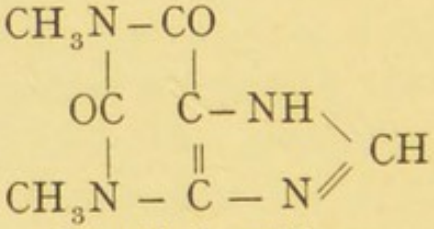
Purine



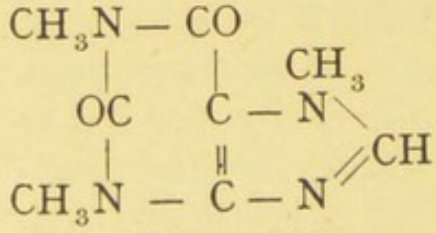
Dioxy-purine, Xanthine



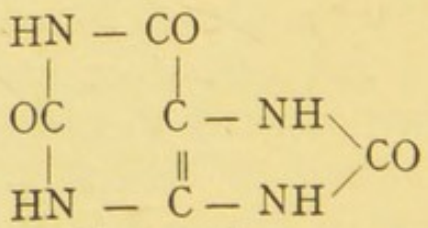
Dimethylxanthine, Theobromine



Dimethylxanthine, Theophylline, Theocine



Trimethylxanthine, Caffeine



Trioxypurine, Uric Acid

These bodies produce diuresis, partly (1) By means of their action in dilating the blood-vessels and increasing the blood-flow through the kidneys, but mainly (2) By a direct stimulating action on the renal epithelium. They act best in cases of cardiac œdema and dropsy, and usually fail in cases where the renal cells or vessels are much diseased or degenerated. In some cases of hepatic disease with dropsy, they are found to produce fair results.

A number of double salts of theobromine have also been prepared, the advantages and disadvantages of which will be considered separately.*

Theobromine. This is the least powerful (except caffeine) of the purine diuretics used in medicine. It is a crystalline powder, only slightly soluble in water; and is absorbed with difficulty. The dose is ·5 gm. (8 grains) or more. It is seldom or never employed.

Zernik† has compared the various theobromine compounds as regards the percentage of that substance which each contains; his results are shown in the following table:—

---

* As the spelling of the names of these compounds is a matter on which some divergence of custom exists, I may, perhaps, be permitted to state that I have throughout retained the final "*e*" for the purine derivatives, as they are somewhat analogous to the alkaloids in their chemical nature and, indeed, are classed with them by some authorities (*vide* J. Schmidt, *Synthese wichtiger Pflanzenalkaloide*, 1900). For the sake of uniformity I have spelt the trade names, such as *theocine*, in a similar manner, though the German manufacturers, of course, conclude all their registered names with the consonant.

† *Apotheker Zeitung*, 1906, p. 898.

	Percentage of Theobromine
Agurine	58·1
Barutine	25·5
Diuretine	49·7
Theophorine	62.5

Theophylline or **Theocine,** considered the most powerful of this group of diuretics, is a white crystalline powder, with a bitter taste, soluble in 180 parts of water at ordinary temperatures. Its action, however, is not prolonged, and it sometimes produces considerable gastric irritation. In two cases of heart disease in which ·3-gm. (5-grain) doses of theocine had been given, death occurred shortly afterwards, and the gastric mucous membrane was discovered, post mortem, to be covered with small hæmorrhages and erosions.* Where gastric disturbance is apprehended, the drug may be given as a suppository.† The initial dose usually recommended is a small one: ·1 gm. (1½ grain) twice daily. It may be cautiously increased, the maximum being ·3 gm. (5 grains) two or three times a day. Some authors advise that doses of ·2 gm. (3 grains) should only be administered every other day, or even at longer intervals.‡ In all cases, the effect of the drug should be carefully watched, and large doses should never be given if small ones are ineffectual.

The insolubility of theobromine and the irritant character of theophylline have caused manufacturers

* Allard, *Deut. Arch. f. klin. Med.*, 1904, No. 5.

† *See p.* 95, footnote.

‡ Rhomberg, *Münch. med. Woch.*, Sept. 29, 1908, p. 2028.

to produce a number of double salts, the chief of which will now be considered.

Diuretine is theobromine-sodium-salicylate ; it is a white soluble powder, with a saltish taste, containing 50 per cent theobromine. It is easily decomposed by carbon dioxide, insoluble theobromine separating out, which may be recognized as a cloudy precipitate in the solutions of the drug. It is incompatible with acids, per salts of iron, bicarbonates, borates, phosphates, etc. The initial dose should be ·5 gm. (8 grains)* three times a day, and this may be gradually increased to 1 gm. (15 grains) four times a day, or even more. It may also be given as an enema. Its administration should not be continued for more than four or five days, after which a pause of two or three days should be made. The salt should be well diluted, and if given in capsules, water should be given at the same time. It is best administered after meals.

Agurine is theobromine-sodium-acetate. It is a white crystalline powder, freely soluble in water, very hygroscopic, and readily decomposed by the action of carbon dioxide. It contains 60 per cent theobromine. It is incompatible with acids, sugars, mucilage, and most alkaloidal reagents.

It is less likely to cause gastric disturbance than diuretine, and as the proportion of theobromine is larger, it should be given in slightly smaller doses. Though less active at first than diuretine, its effect does not wear off so rapidly.

---

* Rhomberg, *loc. cit.*

Theophorine is theobromine-sodium-formate. It contains a slightly higher percentage of theobromine than does agurine, but otherwise closely resembles it in chemical and physical characters. The formate is thought to assist in producing diuresis, and the drug is said to have no irritant action on the stomach if given after food. The dose recommended is ·5 gm. (8 grains) twice daily. Larger doses may cause headache, and are unlikely to produce greater diuresis. It is contraindicated in cases of nephritis.* It appears to possess no special advantages over diuretine or agurine.

Theolactine is theobromine-sodium-lactate. It has physical and chemical properties similar to those of the other double salts, and is intensely hygroscopic. It contains 57 per cent theobromine. The dosage is the same as that of diuretine. Earlier communications† seemed to show that it was specially liable to set up gastro-intestinal disturbances, but in more recent trials this disadvantage has not been noted.‡ It is tolerated for a considerable time by some patients, but appears to have no special advantages beyond this.

Barutin is barium-theobromine-sodium-salicylate. It is a white salt, with a sweetish, alkaline taste. It is especially easily decomposed by carbon dioxide. It contains only 25 per cent theobromine. The dose is ·2 gm. (3 grains) twice daily, which may be

* Cohn, *Deut. med. Woch.*, Aug. 29, 1907.
† Krüger, *Ther. der Gegenwart*, 1907.
‡ *Idem*, *Zentralbl. f. innere Med.*, xxix., 1908, No. 1.

increased to ·5 gm. (8 grains) very cautiously. It should be given in very weak watery solution (1·25 per cent). It appears to present no special advantages, and has been observed to cause cardiac arrhythmia* and also occasionally slight diarrhœa. The presence of a barium salt would tend to constrict the arterioles and raise the blood-pressure, neither of which are usually desirable effects in the class of case for which diuretic drugs are necessary.

Theocine-Sodium-Acetate is a white powder containing about 60 per cent theocine, and soluble in 23 parts of water. It is said to cause less irritation of the gastric mucosa than theocine. The dose is ·2 to ·35 gm. (3 to 5 grains) after meals. Lipowski† recommends that it should be given in the form of a suppository‡ containing ·3 to ·4 gm. (5 to 6 grains).

Of these drugs, diuretine and agurine appear to be most generally useful; at any rate they have been more largely employed than the other compounds. The former produces the greater immediate effect; the latter has the more continued action. The other derivatives are reported as having been

---

* Brat, *Berl. klin. Woch.*, 1905, No. 38, p. 1220.

† *Op. cit.*, p. 54.

‡ All the double purine salts are highly hygroscopic, and consequently, when mixed with cacao butter to make suppositories, they tend to separate out. The suppositories then become brittle, and are liable to break. When this form of administration is specially desired, therefore, the suppositories must be quite freshly made. Enemata, of course, are free from these objections.

occasionally efficacious when these have failed, but they usually have intrinsic disadvantages, as has already been noted, and are perhaps best reserved for specially intractable cases.

Pituitary Extract. This substance, which is considered by Schäfer and others to possess a powerful and specific diuretic action, is described among the drugs acting on blood-pressure (*vide* p. 133).

II.—ANTISEPTICS.

In 1894 Nicolaier introduced into medicine the body known as urotropin, the chemical name for which is hexamethylene-tetramine $(CH_2)_6N_4$. It has two official names, formamine (B.P. Codex) and hexamethylenamine (U.S.P.). Various structural formulæ for this body have been suggested, and in view of the great possibilities for isomeric varieties it is probable, as pointed out by Squire,* that the commercial products differ considerably among themselves in their chemical structure, and that this accounts for the frequent variations observed in their clinical effects. The action as a urinary antiseptic depends on the formation of formaldehyde (formol, formalin) in the urine. A number of substances have since been introduced which are either merely hexamethylene-tetramine itself, or compounds of this with other bodies of an antiseptic character. Various more or less fantastic trade names have been given to these bodies by their

* *Companion to B.P.*, 1908, p. 545.

manufacturers, with the result that an unwary practitioner might very easily prescribe several of them in succession under the impression that in each case he was making trial of a new chemical substance, whereas in each, whatever efficacy it might possess would be due to precisely the same medicament.

Urotropin is also known as **Aminoform, Formin, Formamine, Cystamine, Cystogen, Metramine, Naphthamine, Uramine,** and **Uritone.** It is a colourless, crystalline powder, very soluble in water, the dose of which is ·5 to 1 gm. (8 to 15 grains) several times daily. Owing to the fact that it is liable to set up gastric disturbances, it is recommended* that formamine be given in cachets, followed by a draught of water, or, if a liquid medicine is preferred, combined with syrup of orange, thus :—

℞	Formaminæ	℥ij = 6·09 grams
	Syr. Aurant.	℥iv = 15·0 grams
	Aquam	ad ℥vj = 200 cc.

Dose :—One tablespoonful (20 cc.) in a tumbler full of water.

The **New Urotropin** is a combination of anhydromethylene citric acid with urotropin, and is also known as **Helmitol.** In the B.P. Codex it is termed **Formamol.** It contains 40·7 per cent urotropin, and was introduced owing to the slowness with which the parent substance is decomposed in the body, especially in alkaline media. It is very similar in its physical characters to urotropin, and the dose is the

* *The Prescriber*, iii., p. 31, 1909.

same. It is decomposed by dilute acids, and still more easily by alkalies, and so is thought to act equally well in acid or alkaline urines. It is said to act well in ordinary infections, but not in tuberculous disease, or in the cystitis following spinal lesions.*

Urystamine is urotropin-lithium-benzoate, and is given in drachm doses of the granular effervescent salt, or in 5-grain (·32 gm.) tablets.

Cystopurin is a double salt of hexamethylene-tetramine and sodium acetate. It is a crystalline substance, closely resembling urotropin in its physical characters. **Mesin** is a double salt of hexamethylene-tetramine citrate and lithium citrate. **Saliformin** is a salicylate of urotropin, and is a bitter, soluble, crystalline body, the dose of which is ·5 to 2 gm. (8 to 30 grains) in tablets or solution. It has the same incompatibles as other salicylates, viz., salts of iron and other heavy metals. **Borovertin** is a triborate of hexamethylene-tetramine; it is a crystalline powder giving a bitter solution in water. The dose is 1 to 4 gm. (15 to 60 grains) with or after food, but it is well to begin with small doses (not more than 2 gm. or 30 grains), as in some cases it produces anorexia and vomiting.† Sollmann, in the report to the Council of the American Medical Association to which reference has already been made,‡ details the results of comparative trials of

---

* Bettex, Thèse de Lausanne, *Zeitschr. f. Urologie*, iii., 4, p. 407, 1909.

† Mankiewicz, *Berl. klin. Woch.*, Dec. 3, 1906.

‡ *Jour. Amer. Med. Assoc.*, vol. ii., 1908, p. 818.

these and other antiseptics on human urine. The administration of ordinary doses of hexamethylene-tetramine itself rendered the urine strongly antiseptic. Salol, novaspirin, and sodium salicylate had a similar but much lighter action, while **Glutol** (glutoform, or formaldehyde gelatin), **Citarin** (sodium anhydro-methylene citrate), **Tannopin, Tannoform, Formidin** (a compound of formaldehyde with an iodine-containing salicylic acid derivative), **Ur-a-sol, Boric Acid, Sodium Benzoate, Sodium Sulphocarbolate,** and many other drugs, had no effect in delaying bacterial decomposition. Hexamethylene-tetramine was found to be excreted in the urine unchanged, appearing in the urine eleven minutes after ingestion, and disappearing again after five hours.

Hetraline is a compound of hexamethylene-tetramine with dioxybenzene. This body consists of needle-shaped crystals soluble in 1 in 14 parts of cold water and in alcohol, but much more so in hot water (1 in 4). Its taste is sweetish and not unpleasant. Its value as a urinary antiseptic has been investigated by de Caleya, an abstract of whose thesis is given in the *Lancet* for 1906.* He found that the minimum effective amount daily should be four doses of ·5 gm. (8 grains), in which quantity it does not irritate the tissues, and is about equal in effect to urotropin. According to these and other researches, the bacteria in the urine are not absolutely

* Vol. i., p. 985.

destroyed, but their vitality is considerably lowered, and they show degenerative changes under the microscope. After the urine has become clear, the drug should be continued for some time in order to destroy any spore-forming organisms which may remain. The gonococcus is not destroyed by hetraline.

III.—URIC ACID SOLVENTS.

It must be regarded as very doubtful whether the administration of small quantities of certain drugs by the mouth can possibly render the uric acid circulating in the body fluids more soluble or more easily eliminated by the kidney, or less likely to be deposited as sodium biurate in the tissues. Experiments *in vitro* are not conclusive evidence as to the efficacy of the so-called uric acid solvents, as the conditions obtaining in the body cannot be even remotely reproduced in a test-tube. The difficulty of applying clinical tests to these drugs is increased by the fact that both during the gouty paroxysms and during the intervals between them, great variations in the diurnal excretion of uric acid have been shown to take place under ordinary conditions when no drugs are being administered. For the formation of biurate deposits in the tissues, moreover, it has been shown that some further factor than uric acid retention is necessary, so that the adequate treatment of this condition cannot lie merely in increasing the solubility of the latter body. As regards the test-tube evidence, it has been shown

that the "solvents" lose their power to a great extent in the presence of sodium chloride, which is so widely distributed in all animal fluids.

Bechhold and Ziegler,* as the result of some interesting experiments on the solubility of sodium biurate and uric acid in blood-serum and water, find the latter much more soluble than the former in serum, though in water the reverse occurs. The separation of both bodies from serum is hindered by dilution and by the presence of hydroxyl (OH) anions, or hydrogen, potassium, lithium, and magnesium kations; the sodium kation invariably causes precipitation, and the ammonium kation usually does so. The latter bases should therefore, according to these observers, be avoided in the treatment of gouty persons, and they consider the harmfulness of meat diet to be due, not so much to the purine bodies, as to the excess of ammonium bases which it contains. Fish and vegetables, on the other hand, are richer in potassium and magnesium salts.

The uric acid solvents are of a very varied description chemically, and cannot be classified on any rational basis. They will therefore be considered in the following order, merely for convenience.

1. **Piperazine**

(diethylene diamine, $NH\langle\begin{matrix}CH_2 - CH_2\\CH_2 - CH_2\end{matrix}\rangle NH$.), is a crystalline and highly hygroscopic volatile substance forming an alkaline, but not caustic, solution in

* *Biochem. Zeitschr.*, xx., p. 190, 1909.

water. It cannot be dispensed except in solution, and even then more than twenty-four hours' supply should not be sent out at once. The ordinary dose is ·3 to ·6 gm. (4 to 8 grains), 1 to 2 gm. (15 to 30 grains) being taken in twenty-four hours in water or soda-water. It is apparently very little toxic except in enormous doses; a portion is said to be excreted unchanged in the urine and to prevent the deposition of uric acid and urates; but urine containing it has in reality no special solvent power in this direction. Two derivatives of piperazine have also been tried, namely sidonal and lycetol.

2. **Sidonal** is the quinate of piperazine. It is a white, crystalline, very soluble powder, having a slight acid reaction and taste. The dose is 1 to 1·3 gm. (15 to 20 grains) dissolved in water, five or six times a day. Lewandowsky* considers its action slight and uncertain. It does not influence uric acid formation at all. It is an expensive remedy. In order to meet this objection, a substance called **New Sidonal** or sidonal-neu was introduced. This body is merely an anhydride of quinic acid, and is not a piperazine compound at all. The name, therefore, is somewhat misleading. Its physical characters are very similar to those of sidonal, and the usual daily dose 2 to 3 gm. (30 to 45 grains).

3. **Lycetol** is a tartrate of dimethyl piperazine. It is a white, crystalline powder, only slightly hygroscopic, and its solutions have a pleasant acid

---

* *Zeitschr. f. klin. Med.*, xl., p. 202, 1900.

flavour. The dose is 1 to 2 gm. (15 to 30 grains) in water or aerated water; it should be well diluted. It is incompatible with alkalies.

4. **Piperidine Tartrate** occurs in colourless, soluble crystals, with a pleasant taste. The dose is 1 gm. (15 grains) three times daily.

5. **Lysidin** is ethylene-acetamidine, $\begin{matrix} CH_2N \\ | \\ CH_2NH \end{matrix} \diagdown\!\!\!\!\diagup C.CH_3$, and occurs as white, very hygroscopic crystals, forming alkaline solutions in water. It is a strong base, and so incompatible with acids and many metallic and alkaloidal salts. It is placed on the market in the form of a 50 per cent solution; the dose of the crystals is 1 to 5 gm. (15 to 75 grains) per diem. The solution should be still further diluted with water or soda-water.

6. **Lysidin Bitartrate** is a similar substance, the dose of which, however, is 2 to 10 gm. (30 to 150 grains) per diem.

7. **Urodonal** is a mixture of lysidin, sidonal, and urotropin in a granular effervescent form.

8. **Colchisal** is a preparation put up in small gelatin capsules, each containing ·00025 gm. ($\frac{1}{250}$ grain) of colchicine and ·2 gm. (3 grains) of methyl salicylate.

Bain,* as the result of experiments on the elimination of uric acid in patients treated with these drugs, found that tartrate of piperidine, piperazine,

* *Brit. Med. Jour.*, 1903, i., p. 243.

lysidin, and sidonal, increased the excretion of uric acid in the order named, the last being the most, and the first the least, powerful. Colchisal diminished the excretion, while tetra-ethyl-ammonium hydrate was found in test-tube experiments to owe the solvent effect of its solutions entirely to their alkaline reaction. Ortowski* found that in water at 37·5° C. uric acid was dissolved by the following drugs in the order named: lysidin, piperazine, sodium bicarbonate, urotropin, uricedine.† Neither lysidin, piperazine, uricedine, nor sodium bicarbonate had any influence on the solution of uric acid in urine, nor any physiological action when passed through the body, either in rendering uric acid more soluble or in diminishing its output. Though urotropin has very slight power of holding uric acid in solution in water or urine at body temperature, when taken as a drug the formaldehyde formed unites with uric acid to produce a very soluble compound.

9. **Quinic Acid,** which occurs in cherries, strawberries, and other fruit, as well as in cinchona bark, is a benzoic acid derivative, and occurs as a white, very soluble powder, the dose of which is ·5 gm. (8 grains) several times a day. It has a bitter taste, and is said to adversely affect the teeth. It

---

* *Zeitschr. f. klin. Med.*, xl., p. 331, 1900.

† The formula for this substance is said to be sodium citrate 62·700, sodium sulphate 29·694, sodium chloride 1·206, sodium acetate 1·320, sodium tartrate 1·500, sodium malate 1·450, iron 0·140, sodium pectinate 1·170, extractives 0·820 (Riedel's *Mentor*, 1908).

was thought to prevent the deposit of uric acid in the tissues. Various compounds of quinic acid have been introduced, namely urosin, urol, and quinotropin. The compound with piperazine has already been described.

10. **Urosin** is the lithium salt, and is made up in tablets containing ·45 gm. (7 grains) with carbonate of lithium, sugar, and talc. They are partially soluble in water. Six to ten are to be given daily It appears to be but slightly toxic,* and is described by some authors as a "favourite remedy" in Germany, in spite of the slender experimental evidence in its favour.

11. **Urol** is an addition product of quinic acid and two molecules of urea. It occurs as soluble hygroscopic crystals.

12. **Quinotropin** is a compound of quinic acid and urotropin, containing 78 per cent of the former. The daily dose is 6 gm. (90 grains). Neither of these compounds has obtained much support from exact observations.

13. **Citarin.** (anhydromethylene citrate) is a white powder, somewhat hygroscopic, and slightly acid in taste and reaction. It is easily soluble, the solutions giving off formaldehyde on heating, especially in the presence of alkalies, with which, as well as with acids, it is incompatible. The dose is 1 to 2 gm. (15 to 30 grains) as often as necessary up to five times a day, at any rate for the first few

---

* Weiss, *Wien. klin. Ther. Woch.*, 1904, No. 18, p. 493.

days, after which the dose is better reduced.* It should always be given largely diluted. It is said by many writers to be without any ill effects, but others have noted diarrhœa, gastric disturbances, and diuresis.†

14. **Solurol.** This body is known as thyminic or thymic, or nucleotin phosphoric acid, and is one of the products of disintegration of nucleoproteins. It is a brownish-yellow, amorphous powder, soluble in cold water, and almost tasteless. Its solution has no incompatibles, practically speaking. The dose is ·25 to ·5 gm. (4 to 8 grains) three times a day or oftener. *In vitro*, it has the power of retaining uric acid in solution when that solution is rendered acid at 20° C. It retains its own weight of uric acid in solution, and this property is increased 50 per cent at 37° C. It was thought‡ that under ordinary conditions, uric acid normally circulates in the blood in the form of a compound with nucleotin-phosphoric acid. This, however, has never been proved, and animal experiments do not support the view that the artificial introduction into the blood of a salt of nucleotin-phosphoric acid can render uric acid more soluble or facilitate its elimination by the kidneys. Clinically, nucleotin-phosphoric acid or "solurol" has been employed by several investigators, and notably in this country by Robert Fenner,§ who

---

* Borek, *Klin. Therap. Woch.*, 1907, No. 38, p. 975.

† O. Seifert, *Nebenwirkungen*, Folge iii., p. 52.

‡ Minkowski, *Verhandl. der Cong. innere Med.*, 1900.

§ *Lancet*, 1905, ii., 19; 1908, ii., 1804.

observes that the best effect is obtained in the subacute and chronic cases. He gives tables showing the improvement in general symptoms, but there is no evidence as to the increased excretion of uric acid which is the theoretical cause of the improvement. It is of course quite possible that the drug may do good in certain cases, though its mode of action may be very different from that which it has been supposed to possess, based as this is on several unproved assumptions.

CHAPTER IV.

DRUGS ACTING ON THE Circulation : — (I.) Cardiac Tonics ; (II.) Vasoconstrictors ; (III.) Vasodilators.

DRUGS ACTING ON THE CIRCULATION.

I.—CARDIAC TONICS.

THE introduction of digitalis into practical medicine as a cardiac tonic dates from the last quarter of the 18th century, so that it cannot now be considered a new remedy. But in spite of the large amount of clinical observation which has been bestowed on its effects, and the number of physiological and chemical experiments which have been performed in order to elucidate its action or to determine its composition, it must still be regarded as one of the least accurately known of all the commonly employed medicaments. Owing to circumstances which will be treated with more detail later on, official preparations of digitalis have varied very much in physiological activity, with the result that a number of substances have been placed on the market by various manufacturers which claim to be superior to the usual tincture or infusion in this respect ; and it is on these substances that a few remarks will now be offered. In order, however, to make quite clear the value and nature of these

bodies, it will be necessary to enter a little more fully into the pharmacological chemistry of the digitalis group as a whole.

The active principles of digitalis, which are found in varying amounts in all parts of the plant, belong to the class of bodies called glucosides, the more important of these being the well-known bodies digitoxin, digitophyllin, digitalin, digitalein, and digitonin. Digitoxin and digitophyllin are insoluble in water, but soluble in alcohol and chloroform; the former is by far the most important glucoside of the group, and occurs mainly in preparations from the leaves. Digitalin and digitalein occur in larger quantity in the seeds; the former is soluble in alcohol, but insoluble in chloroform and water; the latter is soluble in water. In watery infusions of the leaves, the glucosides are kept in a kind of solution by the presence of the digitonin, a body belonging to the saponin class of glucosides; these have the power of forming a soapy solution with water by which otherwise insoluble bodies can be extracted. Being insoluble in alcohol, digitonin does not occur in the tincture. Specimens of the leaves vary enormously in their glucosidal content, and moreover, if they are allowed to remain moist after plucking, a ferment contained in them further changes their pharmacological activity by splitting up the digitoxin into its decomposition products. These products are most probably toxic, and certainly alter the efficacy of the drug. To obviate this difficulty, and to secure a uniform strength in

digitalis preparations, it was first proposed to estimate the amount of digitoxin, as being the most important constituent, and from this to standardize the drug. Keller's method was published in 1897, and with modifications is still the recognized procedure. However, it was soon found by means of animal experiment that the physiological activity of the preparations did not vary with their digitoxin content as determined in this way. The reason for this appears to lie partly in the fact that a variable and possibly large part of the glucoside is lost in the process of estimation.

To obtain a reliable standard, therefore, a physiological test must be adopted, but even here many difficulties are encountered, of which an excellent and exhaustive account, together with original experiments, has been recently published by Edmunds and Hale.* They classify the methods into three groups: (1) The toxic method, in which frogs, guinea-pigs, or some higher animals are used, and the minimum lethal dose determined. (2) The frog's-heart method, in which the heart is perfused with a solution of the drug, or otherwise exposed to its action, and the time required to produce systolic standstill is noted. There are various experimental details which require careful consideration in planning tests by this method; and the value of any one observer's results will depend entirely upon the rationale of his particular experimental method.

* *Bull. No.* 48 *Hyg. Lab. U.S. Pub. Health and Marine Hosp. Serv.*, 1909.

(3) The blood-pressure method, in which this is measured in larger animals and the effect of doses of the drug is estimated.

It may be said generally that, according to Edmunds and Hale, the second class of test is the most practicable and useful; but the considerations which lead to this conclusion are of too complicated a character for exposition in this place. No method of physiological standardization is absolutely satisfactory; and when the results obtained by testing a given sample by a number of methods are compared, in spite of a general agreement, there are marked and unexplained discrepancies in many instances.

Enough has been said to show the great difficulties which lie in the way of obtaining an accurately standardized digitalis preparation. We can now, bearing this in mind, consider the various extracts and infusions at present on the market, and also the various so-called pure preparations of the individual glucosides.

Preparations from the Entire Leaves.

1. **Digitalyzatum Bürger.** This is a watery extract to which a little alcohol is added. It is physiologically standardized, and said to be stable. 1 gm. corresponds to 1 gm. fresh leaves, ·2 gm. dried leaves, or ·7 gm. pure digitoxin. The dose is 16 to 20 drops. 25 drops make 1 gm. (·2 gm. or 3 grains of dry powdered leaves).

2. **Digitalis Dialysatum Golaz** is obtained by

expressing the juice from the fresh leaves and then dialysing it so as to contain a uniform amount of the active principle. The dose is 20 drops. Great care is taken in collecting and treating the leaves, but they vary in their yield of glucosides very greatly from year to year, so that in addition a physiological method of standardization is necessary.

3. **Digipuratum** (Knoll) is also a physiologically standardized extract, the active principles of which are insoluble in cold water and acids, but easily so in alkalies. This is thought to prevent its setting up dyspepsia. It is prepared in the form of tablets, each of which is equal to ·1 gm. (1½ grain) of digitalis leaves. It may also be obtained as a powder diluted with milk sugar; both preparations are practically tasteless. Müller,* who has used this preparation for one and a half years in forty cases, states that in full doses the action is prompt and reliable; small doses give more variable effects. Five tablets may be given daily for two or three days, and in ten to fourteen days a total of 3 gm. (45 grains) may be given. The effect is first noticed after two to five days, usually in three, and attains its maximum in from five to fourteen days, usually in ten. When the full effect has been produced, the dose should be diminished, and ·1 or ·05 gm. (1½ or ¾ grain) be given of the powder. Jumon does not think this preparation superior to the ordinary French digitalin.

---

* *Münch. med. Woch.*, 55, p. 2651, Dec. 22, 1908.

4. **Digitalone** (Parke, Davis & Co.) is a physiologically standardized preparation; it contains no alcohol, but 6 per cent chloretone is added as a preservative. The solution is said to be permanent and equal to four-fifths of the amount of the tincture (B.P. and U.S.P.). It is intended for hypodermic use especially, in doses of ·5 to 1 cc. (8 to 15 min.). Edmunds and Hale*, who investigated this preparation, found that it was not stable, but liable to decomposition, the resulting products possessing no digitalis action, and being, moreover, distinctly harmful. A normal specimen appeared to have about half the strength of the official tincture (B.P., or U.S.P.). Zaeslein† reports well on its clinical effect, but Grober‡ does not find it a satisfactory preparation.

5. A number of standardized extracts and tinctures, mainly of American manufacture, were also tested by Edmunds and Hale, who found that the products of the various houses differed from one another considerably in pharmacological activity. Burroughs and Wellcome's concentrated tincture, however, was one of the most active preparations.

Preparations of Pure Glucosides.

Many of these are not, as a matter of fact, pure chemical substances at all.

1. **Nativelle's Digitalin** is a crystalline, bitter

---

* *Op. cit.*

† *Deut. med. Zeitung*, Jan. 14, 1909.

‡ *Wein. med. Klin.*, Aug. 1, 1909.

substance, insoluble in water, but soluble in chloroform and alcohol. Huchard* directs that digitalin (Nativelle) should be given thus: (*a*) In cardiac failure with backward pressure and œdema, 1 mgm. ($\frac{1}{60}$ grain) once or twice in twenty-four hours. If necessary, the same dose or a rather smaller one may be given a week or two later. (*b*) In mitral stenosis with dyspnœa, palpitation, and irregular pulse, $\frac{1}{4}$ mgm. ($\frac{1}{240}$ grain) for three or four days, to be repeated every three or four weeks. (*c*) To maintain regular cardiac action and tone when there are no severe symptoms, $\frac{1}{10}$ mgm. ($\frac{1}{600}$ grain) daily for weeks or months, with an interval of about one week in every four. This preparation is practically identical with (2) **Schmiedeberg's Digitoxin,** which may be prescribed in the same doses. Naunyn and others consider that owing to the sudden supervention of cumulative effect in some cases, the dose of digitoxin should not exceed $\frac{1}{10}$ mgm. ($\frac{1}{600}$ grain).

3. **Digitalinum Verum,** of Kiliani (·65 mgm. or $\frac{1}{100}$ grain) is a somewhat inactive preparation.

Besides these, there are three amorphous preparations which require some notice. Two are known by the name of **Digitalin.**

4. **Homelle and Quevenne's** is a French preparation, and consists of a yellowish-white powder, inodorous, very bitter and irritating to the mucous membranes. The dose is variously stated

---

* *Med. Press and Circ.*, July 14, 1909.

at $\frac{1}{4}$ to 1 mgm. ($\frac{1}{240}$ to $\frac{1}{60}$ grain) and 1 to 4 mgm. ($\frac{1}{60}$ to $\frac{1}{15}$ grain). It is not a good preparation, as its composition is uncertain.

5. **German Digitalin,** the dose of which is also variably given as 1 to 2 mgm. ($\frac{1}{60}$ to $\frac{1}{30}$ grain) and 1 to 5 mgm. ($\frac{1}{60}$ to $\frac{1}{12}$ grain) is soluble in water, and therefore suited for hypodermic injection. It consists of a mixture of glucosides, but contains no digitoxin.

6. **Digalen.**—A fluid preparation has been introduced by Cloetta under this name. He claims that it is a soluble, amorphous digitoxin, but Kiliani* considers that it is a solution of impure digitalein, and Huchard† also states that it is an impure and inconstant preparation. It is sold in the form of a ·03 per cent solution to which 25 per cent glycerin has been added. 1 cc. (17 min.) contains ·3 mgm. digalen, and corresponds to ·15 gm. ($1\frac{1}{4}$ grain) of the dried leaves; it may be given per os or intravenously, but the subcutaneous injection is very painful, and may cause considerable infiltration of the tissues. Besides solubility, the great advantage claimed for this preparation is that, in ordinary medicinal doses, cumulative action never occurs, though with enormous doses it may be produced.‡ It is thus suitable for (*a*) Very acute cases where rapid absorption and immediate effect are required; (*b*) Cases in which a

---

* *Münch. med. Woch.*, liv., p. 886, 1907.

† *Jour. des Prat.*, Dec. 1, 1906.

‡ Freund, *Ther. Monatsh.*, xix., 12, 1905; Cloetta, *Münch. med. Woch.*, Nov. 20, 1906; Achert, *Lancet*, 1908, i., p. 1619.

prolonged course of digitalis treatment is advisable; (*c*) Cases in which, owing to digestive disturbances, no digitalis can be given by the mouth. The usual dose by the mouth is 1 cc. (17 min.) thrice daily; the maximum is 4 cc. (1 dr.), and in cases where protracted treatment is required, Achert considers 6 to 12 min. once or twice a day usually sufficient. Children may be given 1 to 2 cc. daily for two to four days (17 to 34 min.). As much as 3 cc. has been given for three days in a severe case, the patient's age being 11.* For intravenous injection ·5 to 1·0 cc. (1·5 to 3 mgm.) may be given daily; these injections are painless, very rapid in action, and are usually given only once in twenty-four hours. Grober† recommends a rather different dosage. For two days in acute cases he gives 1 cc. (17 min.) thrice daily, and then half that amount. In patients who are accustomed to taking digitalis, the larger dose may be kept up for as long as one week. In chronic cases without degenerate heart muscle, 10 minims or even smaller amounts three times a day are sufficient. He doubts whether digalen is non-cumulative.‡

To discuss the general indications for digitalis or its glucosides would be beyond the scope of this work; but with regard to the choice of a preparation,

---

* Ausset, *Gaz. des Hôp.*, 1908, p. 212.

† *Wien. med. Klinik*, Aug. 1, 1909.

‡ *Vide* also Thomas, *Rév. Méd. de la Suisse Rom.*, xxix., p. 189, 1909.

given the indication for this class of drug, a few brief remarks may be offered. Notwithstanding the advantages as to accuracy of dosage, elimination of side-effects, and rapidity of absorption which are offered by some of the preparations of glucosides, such as digitoxin and perhaps digalen, there are many careful observers* who consider that better results are obtained by the use of a reliable tincture or infusion of the leaves. This is also to some extent supported by experimental evidence,† and is probably, in this country at any rate, the most widely accepted view.

Strophanthus differs from digitalis in having less cumulative action, in being non-irritant (and thus unlikely to cause gastro-intestinal symptoms, though it may cause nausea and diarrhœa), and in not contracting the coronary or pulmonary vessels. Its action on muscle fibre is, however, more generalized, less limited to the heart, more rapid, but less prolonged. Generally speaking, it is a less efficient drug. It has also a sedative effect on the nervous system, and is only very slightly cumulative.‡

Several preparations of the glucosides to which strophanthus owes its pharmacodynamic activity have been produced, all of them named strophanthin. They are usually considered more efficacious than

---

* Janeway, *Amer. Jour. Med. Sci.*, June, 1908; Wood, *Ibid.*, 1908.

† Kakowski, *Arch. Internat. de Pharm. et Thérap.*, xv., 1905.

‡ Focke, *Zeitschr. f. Aerztl. Fortbildung*, Jan. 1, 1909.

the crude drug, but as their composition and dosage differ somewhat considerably, it is very important, in prescribing, to indicate exactly which particular kind is intended to be used. Much confusion, indeed, exists both as to the source and character of these bodies. *Strophanthus kombé* is the official plant, but it seems clear that other varieties are often used. Among these *S. hispidus* and *S. gratus* are important, the former yielding an amorphous and the latter a crystalline glucoside. Not only does the strength of the pharmacopœial tincture vary, but apparently the toxicity of the glucosides varies very considerably, and different conclusions have been reached by different observers. These discrepancies may be partly accounted for by the facts that the tinctures may not always be made from the same variety of plant, that the amorphous glucosides, as met with in medicine at any rate, are not always pure chemical bodies, and that the rate of absorption and the amount remaining unabsorbed in the intestinal canal vary under different circumstances.*

Three varieties of strophanthin may be distinguished, differing not only chemically and physically, but also physiologically† : (1) Crystallized strophanthin, or strophanthin g. (gratus) or strophanthin (Thoms). This is the most toxic, and is chemically identical with ouabain. The British Pharmaceutical Codex (1907) calls this pseudo-

* *Vide* Hatcher and Bailey, *Jour. Amer. Med. Assoc.*, vol. lii., p. 15, 1909.

† Heffter, *Ther. Monatsh.*, 1909, No. 1.

strophanthin. (2) Amorphous strophanthin (Merck). (3) Amorphous strophanthin (Boehringer).

It has been shown experimentally that three times more strophanthin can be administered by the mouth than it is possible to give intravenously,* and even larger discrepancies between the possible dosage by these two methods have been recorded for man (Hochheim). The cause of this is the rapid excretion by the intestine, which would seem to prevent an efficient dose being given in this manner.

Grober† states that the indication for strophanthin is sudden cardiac failure in organic and functional cases. It is useless in nephritis and in neurotic conditions, and always contraindicated where any tendency to embolism exists.

As a general rule, strophanthin should not be injected more than once in twenty-four hours, and never combined with treatment by digitalis. Occasionally rigors,‡ cyanosis, and pyrexia have occurred after intravenous injections, and in one case the injection of ·6 mgm. of amorphous strophanthin was followed by the death of the patient. When taken by the mouth, sickness, diarrhœa with blood and mucus, and headache, have been observed. Liebermeister§ states that eight deaths have been recorded after the administration of strophanthin, apparently attributable to the drug, but Fraenkel

---

* Hatcher, *loc. cit.*

† *Loc. cit.*

‡ Engelen, *Zeitschr. f. Aerztl. Fortbildung.*, Jan. 15, 1909.

§ q. Heffter, *Berl. klin. Woch.*, Jan. 16, 1909.

believes that the danger lies mainly in too frequent administrations, or in the combination of strophanthin with digitalis treatment.*

1. *Strophanthin cryst.* is by far the most powerful and the most toxic of these bodies. It is said to be soluble in 30 parts of absolute alcohol, but this is not always the case. In the quantities required therapeutically, it may be dissolved in sterile salt solution and given by the mouth in doses of 12·5 to 30 mgm. ($\frac{1}{5}$ gr. to $\frac{1}{2}$ grain) in twenty-four hours, the maximum single adult dose being 5 mgm. ($\frac{1}{12}$ gr.). Intravenously the dose is ·5 to 1 mgm. ($\frac{1}{120}$ to $\frac{1}{60}$ grain) in twenty-four hours, or it may be given intramuscularly in similar doses. But even a small dose (less than 1 mgm) may give rise to serious symptoms. In mild cases, suppositories containing 3 mgm. ($\frac{1}{20}$ grain) may be employed. When given by the mouth, the bitterness must be concealed by syrup of orange. Fleishmann,† who has given fifty-two injections to thirty patients, notes that though the results were negative in a few cases, as a rule but one injection was required, after which ordinary treatment by digitalis could be begun.

2. *Strophanthin amorph.* (*Merck*) is a yellowish-white substance, weaker in action than the crystalline, and differing from it in chemical composition. It is not safe to inject it subcutaneously, but ·5 to 1 mgm. ($\frac{1}{120}$ to $\frac{1}{60}$ grain) may be given intravenously or intramuscularly in twenty-four hours.

---

* *Ther. Monatsh.*, Feb., 1909.

† *Rev. de Thérap.*, 76, 10, p. 357, 1909.

3. *Strophanthin amorph.* (*Boehringer*) is similar to the last-named in its physical characters, but is considerably less active physiologically. The dose is ·25 to 2 mgm. ($\frac{1}{240}$ to $\frac{1}{30}$ grain) intravenously or 1 to 3 mgm. ($\frac{1}{60}$ to $\frac{1}{20}$ grain) intramuscularly per diem. By the mouth the dose is 1 to 4 mgm. ($\frac{1}{60}$ to $\frac{1}{15}$ grain) per diem, the maximum single dose in a severe case being 1 mgm. ($\frac{1}{60}$ gr.).

Cactus.—This drug has had a certain reputation as a cardiac tonic. It may be given as a liquid extract in doses of ·06 to ·6 cc. (1 to 10 min.) or as a tincture, the dose being ·1 to ·6 cc. (2 to 10 min.) with a maximal single dose of 1·7 cc. (30 min.). Cactina pellets are said to contain $\frac{1}{100}$ grain of the active principle of *C. mexicana*. There is considerable want of unanimity as to the physiological action and therapeutic value of this drug; most modern authorities state that it has no action whatever comparable to that of digitalis on the heart, Curtin* recommends it mainly as an "adjuvant," and in cases of irregular cardiac action following on the abuse of coffee or alcohol, and also in the tachycardia of Graves' disease. He recommends a mixture containing 3 drops of tinct. digitalis, 5 to 10 drops of the fluid extract of cactus, and 2 or 3 cgms. ($\frac{1}{3}$ gr. to $\frac{1}{2}$ gr.) caffeine. Sayre,† who investigated the properties of the drug for the compilers of the United States Pharmacopœia, found that there being many

* *Rev. de Thérap.*, Jan. 1, 1909, p. 22.
† *Therap. Gazette*, 1906, p. 812.

wild varieties, it was not always easy to obtain samples of the true cactus grandiflorus (*cereus*). Cultivated plants are not considered equal in therapeutic value to the naturally occurring varieties. An alcoholic tincture from the real plant was found to have practically no action on the dog's heart; no alkaloid or definite active principle was discovered in it; and it was found to deteriorate rapidly when kept, owing to the large amount of water, mucilage, etc., in the fresh stems.

II.—VASOCONSTRICTORS.

Vasoconstriction may be required locally to arrest hæmorrhage, or generally to raise the arterial blood-pressure. It may be either a transient or a more enduring phenomenon; and it may be produced directly or indirectly. Many of the drugs which are employed for this purpose have other physiological actions, but as these are fairly easily correlated with their vasoconstrictor effect, the grouping will not be found too artificial for practical utility. Among the newer vasoconstrictors, the following will be considered: (1) *Adrenin and allied bodies;* (2) *Ergotoxin;* (3) *Pituitary extract;* (4) *Derivatives of cotarnine.*

1. **Adrenin.**—The active principle of the medulla of the suprarenal bodies is known by a number of trade names—adrenaline, adnephrin, adrin, epirenan, hæmostasin, hemisine, paranephrin, renestypticin, suprarenin, suprarenalin; and vasoconstrictine. It is a white crystalline powder, with a slightly bitter

taste, easily soluble in hot water; the solutions, however, are unstable, and the active principle is generally combined as a hydrochloride, or added to chloretone. Solutions which have undergone decomposition turn a brownish-red colour. Traces of iron or alkalies, such as may come from contact with glass bottles, and exposure to light and air, are factors in producing this decomposition, with consequent loss of pharmacological action.*

The commercial preparations are usually 1 per cent solutions. It may also be conveniently obtained in tablets. The action of adrenin is on the sympathetic nerve endings, stimulating them to action; thus its effect will be precisely the same as that of an electric current applied to the nerve itself. For instance, the muscle of the bladder wall in a cat is inhibited while the urethral (sphincter) muscle is powerfully stimulated by adrenin; this is exactly the effect obtained by stimulating the hypogastric nerves. On the other hand, in the dog and rabbit neither hypogastric nerve stimulation nor adrenin has any effect. In the ferret and goat both these produce complete contraction of the bladder walls.† Somewhat contradictory reports have been published by various observers on the comparative value of "natural" adrenin, obtained from the gland, and the "synthetic" product which is produced in the laboratory as a pyrocatechin derivative. Dixon‡

* Gunn and Harrison, *Pharm. Jour.*, April 18, 1908.

† Elliott, Report on Action of Adrenin, *Brit. Med. Jour.*, July 15, 1905, p. 127.

‡ *Pharm. Jour.*, April 18, 1908.

and Cushing* both found that the latter, when tested physiologically, was only half as potent as the former, and this was explained by the fact that the artificial product contained two isomeric varieties, one lævorotary and one dextrorotary, whereas in the natural adrenin only the lævorotary form occurs. They came to the conclusion, therefore, that the other (dextrorotary) isomer was inactive physiologically.

This view was criticized by Stoltz†, who was the first to synthesise adrenin, and Dixon's results were attributed to the use of impure solutions. Stoltz quoted the results of several German clinicians and experimenters who found the synthetic body not inferior in potency to the natural. Recently, however, Abderhalden and his pupils have entirely confirmed the earlier work of Dixon and Cushing. These observers obtained specimens of the two isomers in a pure state, and found that the lævorotary variety was active, the dextrorotary practically inert, and a mixture of the two in equal parts (the "racemic" variety) which represented ordinary synthetic adrenin was intermediate in its activity.‡

The vasoconstrictor action of adrenin will now be described, as manifested locally and generally; we shall then proceed to touch on its other physiological effects, and very briefly to indicate its relationships to other bodies in the same group.

---

* *Pharm. Jour*, May 23, 1908, p. 668.
† *Ibid.*, May 16, 1908.
‡ *Zeitschr. Phys. Chemie.* lviii., p. 190, 1909.

(*a*). *Local Action.*—Solutions of adrenin or one of its salts may be applied to raw surfaces to stop hæmorrhage; it constricts the vessels rapidly, and practically no absorption into the general blood-stream occurs. It is also added to solutions of anæsthetic drugs, such as eucaine, to prevent hæmorrhage during operative procedures on the eye. Solutions can be sterilized by boiling without undergoing decomposition. The vasoconstrictor effect has also been employed in the treatment of hay fever and other congestive conditions of the nasal mucosa. The solution is applied by means of a spray, or by swabbing over the affected surface with wool tampons. It has also been advised internally for hæmatemesis.

The strengths employed vary. Hypodermically 1–100,000 will blanch the tissues. For mucous membranes 1–5,000 to 1–10,000 is used; to check hæmorrhage from cut surfaces, stronger solutions, up to 1–1,000, may be necessary. When given for hæmatemesis, ·25 to 1·25 cc. (5 to 20 minims) of 1–1,000 solution may be administered, and the dose repeated at intervals.*

Sir James Barr has for some years used solutions of adrenin for intrapleural injection, combined with sterile air, after the withdrawal of a serous effusion. He has described his method in detail in the Bradshaw Lecture for 1907.† After the fluid has been

* For the dosage of adrenin when injected into the spinal canal, *vide p.* 189.

† *Brit. Med Jour*, 1907, ii, p. 1293; see also *Brit. Med. Jour.*, 1904, i., p. 649.

evacuated and air introduced, he injects 4 cc. (1 drachm) of 1–1,000 adrenin diluted to two or three times its bulk with sterile salt solution. This contracts the pleural vessels, which are innervated by the sympathetic, and diminishes the tendency to reaccumulation of the fluid. Dr. Ewart, in a modification of this treatment,* suggests that paracentesis may in some cases be avoided by injections of adrenin solution. In a case he describes, ·5 cc. (8 minims) of 1–1,000 solution were injected at intervals of a few days, absorption taking place, and convalescence being established in ten days. The author considers that larger amounts might with advantage be employed, but that it is important in all cases to withdraw a little of the serous fluid into the syringe containing the solution, in order to make certain that the latter will not pass directly into the lung tissue.

(*b*). *Taken by the Mouth*, adrenin solutions have practically no action on the general blood-pressure, as the drug is decomposed in the stomach; subcutaneous injections, moreover, cause local vasoconstriction only. Dixon has given to a man 60 minims of the 1–1,000 solution, and has injected 1 minim of a similar strength hypodermically, without affecting the general arterial pressure.† Such a strong solution, however, should not be employed in practice, as there is considerable danger of permanent damage to the tissues due to the local

* *Brit. Med. Jour.*, 1906, i., p. 973.
† *Lancet*, 1908, i., p. 826.

vasoconstriction. It appears to be destroyed *in situ*. Intravenously, it produces a contraction of the muscular walls of the arterioles, most marked in those in which the development of the vaso-constrictor fibres of the sympathetic is greatest. The result is a general rise of blood-pressure.

The dose is usually raised by varying the strength of the solution 1–100,000 to 1–1,000. One minim of the stronger solution will cause a general rise of blood-pressure. The vessels most constricted are those in the splanchnic area, then those in the limbs, while the vessels in the brain are hardly affected, and the coronary and pulmonary vessels not at all. The blood therefore tends to collect in the latter, so that there is some congestion of the lungs, and somewhat less marked congestion of the brain. Thus adrenin should never be injected in order to control hæmorrhage in these areas. The employment of adrenin has been, as a matter of fact, almost entirely restricted to local operations. Its internal use is likely to be of considerable value, however, in cases of severe shock, as it not only constricts the arterioles but also stimulates the heart. Elliott* notes that in every vertebrate animal examined, the beat of the auricle is both augmented and accelerated. In mammals the ventricle also is stimulated. The action, however, may be masked by high blood-pressure and cardiac dilatation, which if extreme may cause the beat to be slowed. Small

* *Loc. cit.*

doses repeated at intervals, may be given (2 or 4 drachms, or 10 to 20 cc. of a solution 1–100,000) or, as Mummery and Symes* recommend, the continuous injection of a 1–50,000 solution may be tried. By this means the amount passing in at any time can be regulated, and any blood-pressure which is desired can be maintained with a minimal dose. A single injection only produces a very brief rise, lasting but a few minutes.

Crile† has recently advocated the direct injection of a dilute adrenin solution into an artery to avoid the retention of the drug in an enfeebled and dilated right heart. His method may be shortly described as follows: The patient being in the prone position, rapid rhythmical compressions of the chest are made by means of a hand placed on each side of the sternum. A cannula is inserted into any convenient artery, pointing *towards* the heart (i.e., *against* the blood-stream), and warm saline, sterile water, Ringer's or Locke's fluid, or even tap water, is allowed to flow in by a funnel and rubber-tube arrangement. When the flow is established, 1 to 2 cc. (15 to 30 min.) of 1–1,000 adrenin solution is injected by passing the point of the needle through the rubber tube, and the dose is repeated in one minute if necessary. Meanwhile, the rhythmical compressions of the thorax are still more vigorously practised. When the pressure in the coronary arteries has by these means been raised to 40 mm. of mercury, the cardiac

* *Brit. Med. Jour.*, 1908, ii., p. 786.

† *Amer. Jour. Med. Sci.*, vol. cxxxvii., p. 469.

contractions will probably begin again, according to Crile, and when these have been completely established, the cannula is to be withdrawn or blood will be forced up into the funnel. An auxiliary measure consists in firmly bandaging the abdomen and limbs over cotton-wool.

O. Seifert* has collected from the literature a number of cases in which untoward symptoms followed the use of adrenin, and one which resulted fatally. He notes that it is contraindicated in glaucoma and in aortic disease, but does not allude to its disastrous action in bleeding from the cerebral or pulmonary vessels. Toxic symptoms, such as headache, vomiting, rigors, faintness, palpitation, and collapse, have occurred after its application to mucous membranes and wounds. Locally, delayed healing of wounds, and necrosis, are observed; and in some persons a marked idiosyncrasy exists. A curious case of chronic poisoning is reported by Feiler. The patient had for six months instilled adrenin solution into the conjunctiva several times daily, and the symptoms of intoxication were palpitation, shortness of breath, polyuria, slightly yellow tinging of the conjunctiva, and considerable increase in fat. The author does not mention glycosuria, which is a common and well-known result of adrenin poisoning

Carleton† has found an ointment containing 1 part in 1000 of adrenin useful in relieving the pain of neuralgia. The amount used is only ·06 to ·12 cc.

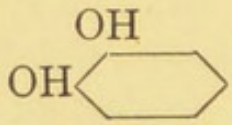
* *Op. cit.*

† *Therapeutic Gaz.*, May, 1907.

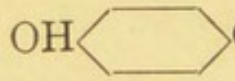
(1 or 2 min.) by inunction; in the case of the sciatic nerve as much as ·18 cc. (3 min.) may be used. This quantity is not sufficient to produce ischæmia; in fact the smallness of the dose suggests that the effect, when produced, is rather psychical than physiological.

It had been thought on theoretical grounds that adrenin might prove of value in diabetes, but Noel Paton* has shown by careful clinical trial that no beneficial result accrues, in fact even so small a dose as ·016 mgm. per kilogram bodyweight caused a marked increase in sugar excretion.

Recently two substances which are chemically closely allied to adrenin have been isolated by Dale from ergot;† one of these has been produced on a commercial scale under the name of tyramine. Adrenin itself is a compound derived from catechol or pyrocatechin, $C_6H_4.(OH)_2$ 1 : 2. The relationship of these bodies will be seen by considering the following structural formulæ:—



Pyrocatechin



Adrenin

Tyramine

Tyramine is the chief constituent of the watery extract of ergot, and is also a decomposition

* *Scottish Med. and Surg. Jour.*, Dec., 1904, p. 492.

† Dale and Dixon, *Jour. of Physiol.*, xxxix., p. 25.

product of tyrosin (*p*-oxyphenyl-amido-propionic acid)

Tyrosin

Its physiological action differs from that of adrenin mainly in being slower in onset and weaker, though more prolonged; it may, however, be given hypodermically or by the mouth, a point of some practical importance. The hypodermic dose is 5 mgm. (gr. $\frac{1}{12}$) dissolved in distilled water or salt solution.

2. **Ergotoxine.**—This body, which has been isolated from ergot,* is held to be the active principle on which most of the ergot preparations depend, though in watery extracts the bodies of the adrenin type already described contribute to the physiological effect. The previously described bodies known as cornutine and sphacelotoxine owe their activity to ergotoxine. It is a feebly basic body, amorphous and insoluble in water, but forming soluble crystalline salts. Prolonged boiling partly converts it into an anhydride, an inert substance identical with that described by Tanret under the name of ergotinine, and at first thought to be the active principle of ergot. Ergotoxine produces a prolonged contraction of the arterioles, and also increases uterine movements; the effect is slight when the drug is given by the mouth, more marked when it is injected hypodermically, and best seen when it is thrown into a vein.† The action has

* Barger and Carr, *Jour. of Chem. Soc.*, xci., 1907, p. 337.

† Cronyn and Henderson, *Jour. of Pharm. and Exp. Therap.*, Aug., 1909.

now been carefully studied,* and it has been shown that, whereas small doses stimulate the uterine contractions and cause vasoconstriction with a rise of blood-pressure, large doses paralyze the myoneural junctions, which are stimulated by adrenin, thus producing vasodilatation and a fall of blood-pressure.

The doses for an adult are ·6 to 1·2 mgm. ($\frac{1}{100}$ to $\frac{1}{50}$ grain) as a single injection, or 5 to 10 mgm. ($\frac{1}{12}$ to $\frac{1}{6}$ grain) in twenty-four hours. Dr. Sharp considers the alkaloid chiefly valuable as a rapid vasoconstrictor,† and in other cases prefers the liquid extract of ergot. As with adrenin, the pulmonary, cerebral, and coronary vessels are not constricted, and the brain and lungs consequently become congested.

A mixture of ergotoxine with tyramine and the other active principles of ergot has been introduced under the name of **Ernutin**. The amount of ergotoxine contained in it is determined by finding how much must be injected in experimental animals to produce paralysis of the myoneural junctions. This point is determined by the injection of adrenin, which, if the myoneural junctions are intact, will produce a rise of blood-pressure, whereas if they are paralyzed a fall results. Ernutin is a fluid, the dose of which is ·25 to ·5 cc. (5 to 10 mins.) intravenously or hypodermically, with a maximum of 2 cc. (30 mins.) in one hour; 2 to 3·5 cc. (30 to

* Dale, *Jour. of Physiol.*, xxxiv., 1906, p. 163.

† *Lancet*, Feb. 1, 1908. (Leeds and West Riding Med.-Chir. Soc.)

60 mins.) may be given by the mouth three or four times a day for some days.

3. **Pituitary Extract.**—An extract of the posterior lobe of the pituitary body produces a general vasoconstriction, with consequent rise of arterial blood-pressure. Unlike adrenin, pituitary extract does not act only through the sympathetic end-organs (the myoneural junction); it consequently constricts the pulmonary and coronary vessels as well as the splanchnics. The pulmonary vessels, however, being poorly supplied with unstriped muscle, do not respond vigorously to this or any other drug. It also causes contractions of the spleen and uterus, and was found by Schäfer to have a specific diuretic action. Haughton and Merrill,* however, find that while contracting the coronary and other arteries it dilates the renal, and to this they ascribe whatever diuretic action it possesses. Pal† has made similar observations. According to Mummery and Symes,‡ there is a slight preliminary fall in blood-pressure due to slowing of the heart, and then a gradual and prolonged rise which may last for upwards of an hour. A second dose has practically no effect, but adrenin may be given, and will prove efficacious should the pressure require to be again raised.

A few cases have already been published in which pituitary extract has been used with good results,

* *Jour. Amer. Med. Assoc.*, Nov. 28, 1908, p. 1839.
† *Wien. klin. Woch.*, 1908, p. 1793.
‡ *Loc. cit.*

mainly in post-operative shock.* The dose of the extract usually given corresponds to ·1 to ·2 gm. of the fresh gland. It is hardly absorbed at all by mucous membranes, and is destroyed by pancreatic digestion; it cannot therefore be given by the mouth. Subcutaneous injections cause too severe a local reaction, so the drug is given by the intramuscular method; ·5 to 1 cc. (8 to 16 mins). of a 20 per cent solution of the extract, may be administered. The active principle is not destroyed by heat, and solutions are thus easily sterilized by boiling. Burroughs & Wellcome have placed sterile ampullæ on the market, each of which contains a 1-cc. dose. The effect lasts for many hours (six to fifteen) and passes off gradually. Saline injections, per rectum or otherwise, should be simultaneously administered.

A full account of the action of the pituitary body and of its extracts has been compiled by Delille.† He states that its use is contraindicated by high arterial pressure, but that under the contrary conditions it may be given to improve the general vasomotor tone, to promote sleep and appetite, and to better the nutrition of the body. Especially he recommends it in cases of Graves' disease, paralysis agitans, and delayed development. The extract of the entire gland should be employed, as being much less expensive and hardly less efficient than

* Blair Bell, *Brit. Med. Jour.*, 1909, ii., p. 1609; Wray, *Ibid.*, p. 1745.

† *L'Hypophyse et la Médication Hypophysaire.* Paris: Steinheil, 1909.

that made from the posterior lobe only, the amount given per diem being the equivalent of half the fresh gland of the ox.

4. **Stypticine** and **Styptol.** — The substances introduced under these names are derivatives of cotarnine, an alkaloid occurring in opium, and closely related chemically to hydrastinine, which is a decomposition product of hydrastine, the alkaloid of *Hydrastis canadensis*. Stypticine is cotarnine hydrochloride, and styptol is cotarnine phthalate; both are yellow crystalline powders, soluble in water, and are prescribed in tablets, or in a 10 per cent solution. The dose in either case is ·05 to ·1 gm. ($\frac{3}{4}$ to 1$\frac{1}{2}$ grain) three to five times daily. The precise mode of action of these drugs is not quite clear, but apparently they directly affect unstriped muscle. They are usually prescribed in uterine hæmorrhages of all kinds, whether due to fibroids, inoperable cancer, subinvolution, or climacteric irregularities; and are probably useless for any other sort of bleeding. Three ·05-gm. tablets may be swallowed every day for a fortnight before the hæmorrhage is expected, and the dose doubled during the period; or if necessary, similar doses may be administered hypodermically during the occurrence of bleeding. Nervous excitement, sickness, headache, and diarrhœa have very occasionally followed the use of these drugs (Seifert). These drugs have an advantage over hydrastinine in that they are considerably less expensive, the latter drug costing ninepence a grain in England and somewhat less in Germany.

III.—VASODILATORS.

The action of the nitrates and nitrites is now well known and adequately dealt with in the ordinary text-books of pharmacology. A substance known as **Amenyl** has recently been used in Germany as a remedy for amenorrhœa* which, it has been thought, might prove useful in cases of hyperpiesis, as it dilates the vessels and so lowers arterial pressure. Chemically it is methyl-hydrastimide.

It is stated to have no action on the heart, except in toxic doses, and to be harmless in cases of uncompensated valvular disease. The usual dose is ·05 gram (¾ gr.) twice daily.

---

* Falk, *Ther. Monastsh.*, xxiii., 11, 1909; Freund, *Ibid.*

CHAPTER V.

HYPNOTIC DRUGS :—(I) Those which are dangerous ; (II) Those presenting no advantages ; (III) Mild Hypnotics ; (IV) Medium Hypnotics ; (V) Powerful Hypnotics.

HYPNOTIC DRUGS.

IT hardly falls within the scope of this work to indicate the special or general considerations which should be held to justify the use of hypnotic drugs; still less to set out the various theories of their mode of action. By far the most complete clinical observations on hypnotics are those made in asylums, and it is, no doubt, in this class of practice that their exhibition is most frequently demanded. In acute illnesses, however, when other measures, such as cold sponging, fail or are inapplicable, and in certain other cases where symptomatic treatment is all that is possible for the time being, hypnotic drugs have been, and doubtless will continue to be, quite reasonably employed. A large number of synthetic hypnotics is now on the market and, speaking generally, they have been found satisfactory clinically. They vary, however, considerably, both in their chemical composition and in their physiological effect, so that instead of increasing the dose of a mild hypnotic if it fails to produce sleep, the

physician may employ another of greater strength, and thus avoid, perhaps, unpleasant after-effects. It has also been noticed clinically, that in cases where hypnotic drugs have perforce to be employed more or less continuously over long periods, a change from one to another is sometimes advisable, though here, too, there are special indications to be considered. Certain hypnotic drugs are ineffective when used as substitutes for others, whereas a third class may under the same conditions be employed with advantage.

As has not infrequently been pointed out, the ideal hypnotic has not yet been discovered. It should be a pure chemical substance, not inconveniently unstable, and with no tendency to polymerization or rearrangement of its molecules. It should have no unpleasant taste, and should be easily soluble and quickly absorbed. Its action should be absolutely selective, only the highest cerebral cells being affected even by large doses, and the elimination should be rapid and complete, leaving no trace of cumulative or delayed action. The sleep produced should be quiet, dreamless, and natural, and there should be no by-effects, such as digestive disturbance, or after-effects, such as heaviness or headache.

Many known hypnotics fulfil some of these conditions fairly well; as a rule, however, those which produce the most natural sleep and are most free from undesirable by-effects are those whose action is mildest, and therefore only to be relied on in the

more trifling cases of insomnia. Others again owe their reputation for safety to the fact that they are but slowly absorbed. In these cases if, owing to the presence of pain, delirium, or other disturbing influence, the dose is much increased, the increase in hypnotic effect will not be proportionate, but owing to slow absorption a prolongation of the drowsiness produced may be expected.

The usual classification of hypnotic drugs is that elaborated by Fraenkel, according to which they are arranged in three groups according to their chemical composition. The hypnotics are thus divided into (1) Those containing a halogen element (chlorine or bromine) to which the hypnotic effect is due; (2) Those in which the hypnotic action is determined by the presence of alkyl groups, especially ethyl (C_2H_5); (3) Those which are chemically aldehydes (containing the CHO group) or ketones (containing the CO group).*

No very marked physiological qualities can be said to distinguish these groups; mild and powerful, soluble and insoluble, dangerous and safe, will be found in all alike. A more practical method of grouping will therefore be adopted here. In the first two divisions will be placed those drugs which are definitely dangerous or which present no particular advantages. The remaining three groups will include the mild, medium, and powerful hypnotics respectively.

---

* *Vide* p. 171

I.—DANGEROUS HYPNOTICS.

1. **Tetronal** belongs to the group of which sulphonal and trional are better known and more useful members. They all contain sulphur, but it is not to the presence of a sulphur-containing group that they owe their hypnotic action, but to the ethyl radicles (C_2H_5), of which sulphonal contains two, trional three, and tetronal four.

The number of ethyl groups seems to determine the strength of the hypnotic action, though it is possible that the relationship is an indirect one, and immediately conditioned by physico-chemical properties.

Tetronal is a crystalline body, but little soluble in cold water, and therefore best given in a hot liquid such as tea. It may also be given in a cachet, and followed by a draught of hot water in order to facilitate its solution in the stomach. The dose is ·6 to 1·3 gm. (10 to 20 grains). It has never been very largely employed, and Ziehen* considers it altogether too dangerous a drug for general use. There are other equally powerful hypnotics which are considerably safer, and it will not be further considered here. Its toxic effect resembles that of trional or sulphonal.

2. **Isopral.** This hypnotic is a white, crystalline powder, slightly soluble in water (1 : 33 at 60° F.) ; its solutions have a very unpleasant and burning taste and camphoraceous odour. The dose is ·5 to

---

* *Deut. med. Woch.*, Apr. 2, 1908.

1 gm. (8 to 15 grains); 2 gm. (30 grains) should be considered the maximum in refractory cases. It may also be given in lozenges, as an enema (3 to 4 gm.) or suppository, or rubbed into the skin. For the last mentioned method of application Foerster's* formula is: Ol. ricini, 10; Alcohol absol., 10; Isopral, 30. The dose is 1 to 5 gm. (15 to 75 grains) of isopral. The area of skin should subsequently be covered with guttapercha and a bandage to promote absorption. This method of administration succeeds in only one-third of the cases. Ollerenshaw† places it among the medium hypnotics in point of strength. It induces some ten to twelve hours' sleep, and is prompt in action (ten to twenty minutes in man, sooner in animals). It cannot, however, be regarded as a safe hypnotic.

Probably owing to the presence of three chlorine atoms, it has a depressant action on the heart. Even in small doses it causes cardiac disturbance, and lowers the blood-pressure by its action on the vasomotor centre. It is also liable to cause irritation of the gastric mucosa, especially when given in solid form. Severe headache, faintness, gastric pain, and occasionally urticaria may occur. Petschnikow‡ considers it the most harmful of all the synthetic hypnotics as regards the heart. He arranges the following drugs in order, beginning with the most

* *Münch. med. Woch.*, 1905, No. 20.
† *Med. Chron.*, vol. xvi., p. 17, 1908–9.
‡ *Wratsch*, 1904, No. 27.

toxic: Isopral, chloral hydrate, hedonal, paraldehyde, veronal, urethane.

Isopral is apparently rapidly excreted, and is therefore not cumulative, but tolerance is established after a time and the hypnotic effect ceases.

3. **Chloralose** is a compound of chloral hydrate and glucose. It is soluble in water, but usually given in cachets, owing to its unpleasant taste. The dose is ·13 to ·5 gm. (2 to 8 grains). It is more likely to disturb digestion than chloral, which it otherwise resembles in its effects. It differs from other hypnotic drugs in exaggerating the reflexes and producing convulsions. Owing to the fact that it may produce excitement and tremor, possibly owing to the formation of a second body, para-chloralose, which has no hypnotic action, it must be regarded as an unsatisfactory drug. It also is a cardiac depressant, and is contraindicated in cases of heart disease (Bradbury).

4. **Chloralurethane** (*ural, uralium*) exists as white shining crystals, the dose of which is 1 to 3 gm. (15 to 45 grains). An alcoholic solution, of which the dose is ·8 to 1·7 cc. (15 to 30 min.), is known as *somnal.* It is an uncertain and dangerous drug, its toxic action lasts longer than its hypnotic effect, and it frequently gives rise to digestive disturbances.* In animals, paralysis of the hind quarters occurs after effective doses; diarrhœa, diuresis, salivation, itching, and respiratory disturbances occur if the drug is pressed.

* *Lancet,* 1891, i., p. 46.

II.—HYPNOTICS HAVING NO SPECIAL ADVANTAGES.

The drugs in this group, though not specially dangerous, present certain disadvantages in some cases, and in others are devoid of any special advantages. They may be considered under three sub-headings :—

1. **Addition Products.**—By this is meant drugs which are produced by combining two chemica substances in their molecular proportions to form a third substance which will have the properties of both its components. Such bodies are obviously of very little value, because, should it be desirable to combine two drugs, this can be done quite as effectually and much more cheaply by ordering both in one prescription. An example of this class is found in *hypnal*, a compound of chloral and antipyrin, the dose of which is 1 gm. (15 grains) in a cachet. Its toxic dose is the same as that of chloral.

2. Certain drugs, sometimes classed as hypnotics, are in reality sedatives or analgesics, and are better employed for these purposes. Such are **Trigemin,** a compound of butyl-chloral and pyramidon, and **Brometone,** a bromine derivative analogous to chloretone ; the former is similar to pyramidon in its action, and the latter resembles the bromides.

3. **Propion** and **Hypnone** are chemically closely allied bodies, belonging to the group of ketones. The former is somewhat insoluble and very nasty, whilst the latter is unreliable in action and often

causes headache. Moreover, tolerance is very quickly established.*

III.—MILD HYPNOTICS.

1. **Urethane,** a white, crystalline powder, soluble in water and almost tasteless, is probably the mildest known hypnotic. It is mainly used for children (v. Jaksch) to whom ·1 gm. (1½ gr.) may be given for every year of their age up to 15. It has practically no action on the respiratory centre, the blood-pressure, or the pulse-rate. Diuresis is produced, as in the case of all urea derivatives. Sleep occurs in twenty minutes to half an hour. The repeated dose for adults is 2 to 4 gm. (30 to 60 grains); 6 gm. (90 grains) may be given as a single dose. A little syrup should be added to its solution, as the taste is somewhat bitter. As an enema, much smaller doses suffice; ·25 to ·75 gm. (4 to 12 grains) as a 30 per cent solution in water, is an effective quantity.

2. **Hedonal,** a derivative of urethane, is a more powerful hypnotic. It is much less soluble than urethane, and has an unpleasant, burning taste. It may be rendered more soluble by the addition of brandy or spiritus vini rect. to the prescription, and the taste may be improved by cinnamon; or it may be given in a cachet, but in this case it should be followed by a hot drink of some sort, or the hypnotic action may be delayed. The bulk of the powder

---

* O. Seifert, *Würtzburger Abhandlungen*, i., 1, p. 10.

however, prevents this from being a convenient method of administration.

The dose of hedonal is usually given at ·5 to 1 gm. (8 to 15 grains), but the latter is generally found a minimum for adults; 2 gm. (30 grains) are often required for adult men, who as a general rule require larger doses than women; as much as 4 gm. (60 grains) has been given in cases where there is much excitement. Hedonal may also be given per rectum. Circulation, respiration, and temperature are practically unaffected by moderate doses, and generally speaking, the main disadvantages of the drug are its insolubility and its unpleasant taste. Sleep is usually obtained within thirty minutes and lasts seven hours or so; if the drug is in solution, a more rapid action may be produced. On the whole, undesirable by-effects are not common. They are, in the first place, digestive disturbances, such as prolonged hiccough on waking, vomiting, nausea, and diarrhœa; next, cerebral symptoms such as giddiness, headache, numbness, and occasionally excitement; and thirdly, miscellaneous effects, such as slow pulse, low temperature, and diuresis. Eight grams (120 grains), taken with suicidal intent, produced gastric pain and vomiting in fifteen minutes, with symptoms of collapse, from which, however, recovery took place.*

Occasionally, hedonal produces drowsiness on the following day, but this should not occur if the drug is taken in solution. Caution in its use is advisable

* Lederer, *Wien. klin.-ther. Woch.*, 1904, No. 16.

in cases of heart disease and arteriosclerosis, and it is said to be ineffective in senile insomnia. On the whole, hedonal is a safe and efficient hypnotic in cases where there is no pain and no mental excitement, such as those of "simple" insomnia, mental depression, alcoholism, or neurasthenia. Its effect may be enhanced, where necessary, by combining with it small doses of morphia or pyramidon to allay pain and allow the hypnotic action to come into play.

3. **Amylene Hydrate** is a colourless liquid, with a burning taste and characteristic aromatic odour; it is very hygroscopic, and is decomposed by the action of light, from which it must therefore be carefully protected. The dose is 40 to 60 min. (2·0 to 3·5 cc.), but larger doses have been given occasionally (up to 5 cc.). The unpleasant taste may be concealed by liquorice or orange-flower water, or the administration may be by means of gelatin capsules per os, or with mucilage per rectum. It is not suited for intravenous or hypodermic use, though it has sometimes been given intramuscularly. Its indications are practically the same as those for hedonal, and its main advantage is its prompt action (fifteen to twenty minutes). The sleep produced should last about six hours, but the duration of the hypnotic effect is not very constant. Tolerance is established in about a week. Though serious disturbances are uncommon, slighter inconveniences not infrequently occur even after moderate doses. These are mainly digestive derangements, such as gastric pain, flatulence, and

occasionally vomiting and constipation. The disagreeable taste is sometimes perpetuated by the eructations which occur, and is apt to be perceptible on the following morning. Larger doses may give rise to feelings of heaviness and congestion in the head, dizziness and faintness. Increased diaphoresis, bronchorrhœa, flushing, and erythemata have been observed; a weak, irregular pulse (either fast or slow), a fall of temperature, and mental excitement, are among the more alarming symptoms which may occur after large doses.

A case of poisoning (after 27 gm.) has been recorded, which, however, was not fatal. The treatment was general stimulation by means of mustard plasters, injections of ether, and enemata of wine and milk.* In another case, 8 gm. produced vomiting in fifteen minutes, and later on drowsiness, pains in the head, and rigors, but recovery eventually took place.†

4. **Chloralamide** is a combination of chloral and formamide, and occurs in the form of a white, very insoluble powder. It must be dissolved in warm spirit (brandy or whisky ℥ss to ℥j) before being taken, but heating above 60° C. (150° F.) must be carefully avoided, in order that the drug may not be decomposed. It is incompatible with alkalies and alkaline carbonates, but may be given with dilute acids (Savage). Spiritus ætheris nitrosi is an excellent solvent (Ollerenshaw). It should never be given in cachets, as its action is then often delayed

* Anker, *Ther. Monatsh.*, 1892, No. 11.
† Lederer, q. O. Seifert.

for twelve or fourteen hours. The maximum single dose is 4 gm. (60 grains); usually, half this amount is ordered, one hour to one hour and a half before sleep is required. The effect lasts from four to eight hours. In the alkaline body fluids chloral is slowly split off, and ammonium formate left, which has a stimulant action on the circulation. Chloralamide is thus one of the safest hypnotics, and is specially indicated where there is cardiac weakness. It occasionally produces headache, faintness, nausea, loss of appetite, and diarrhœa. A few German authors consider it contraindicated in uncompensated cardiac disease, but this is not the view generally held in this country.

The absence of unpleasant taste, and its comparative stability and safety, render chloralamide a most useful drug for the milder degrees of insomnia. Ollerenshaw* considers that the delay which not infrequently occurs before its action is established is really its only disadvantage. He notes that, in children, 20-grain doses often act on the night following that on which the dose was administered.

5. **Dormiol,** or amylene chloral, is a compound of one molecule of chloral with one of amylene hydrate, and occurs as a colourless fluid with a burning taste and aromatic odour. It is only miscible with water *secundum artem*, and is placed on the market in 50 per cent and 10 per cent solutions. The single dose is ·5 to 2 gm. (8 to 30 min.), but larger doses may

* *Loc. cit.*, p. 9.

be necessary, though it is not thought advisable to exceed 3 gm. (45 min.). The unpleasant taste may be concealed with liquorice or syrup of orange, or the drug may be given in gelatin capsules, of which some are sold containing ·5 gm. each. It may also be given in mucilage as an enema, but it is not suitable for hypodermic injection, being far too irritant. Sleep occurs in about half an hour, and lasts 6 to 7 hours. The indications for its use are the same as those for the other members of this group, and it is said not to depress the heart or respiration. It is also especially indicated in cases of phthisis, as it has some action as an antihydrotic. Digestive disturbances, such as occur after amylene hydrate, are not very infrequent, and are less easily got rid of when the drug is given in capsules, i.e., undiluted. Headache, faintness, singing in the ears, and distressing dreams sometimes occur. Occasionally a sort of intoxicated condition is produced, and drowsiness during the following day has also been noted. Tolerance appears to set in after a week or ten days.

6. **Viferral,** a white, crystalline powder, with a bitter taste, easily soluble in hot water, is chemically a compound of pyridine with a polymer of chloral. It is insoluble in dilute acids, and so probably passes through the stomach unchanged; it is claimed for it that, owing to the polymerization, the irritant action of chloral on the gastric mucosa is annulled.*

* Witthauer and Gärtner, *Ther. Monatsh.*, Mar., 1905.

The reports on the practical value of this drug are but few ; it appears to be a mild hypnotic, suitable for cases in which hedonal might be given. The dose should be not less than 1 gm. (15 grains) and not more than 3 gm. (45 grains). The taste is unpleasant, so that the drug may with advantage be given in cachets, to be followed by a drink of hot water, or spirits and water. There are too few reports published to make sure of its harmlessness. Headache, etc., has been observed to occur after its use, but only further experience can decide whether it presents any advantages over the other members of this group.

Speaking generally, the substances included in Group III. may be described as safe hypnotics in moderate doses. They are suitable for cases of simple insomnia, and for mental or nervous cases where there is not much excitement. The insomnia which accompanies fever has been treated by them, but there are better methods of dealing with this condition. When pain or mental excitement are present, they can do no good. With the exception perhaps of chloralamide and viferral, they are all liable to upset digestion, and occasionally produce headache and other nervous symptoms. Hedonal, amylene hydrate, dormiol, and viferral are unpleasant to take, chloralamide and urethane are practically tasteless. Chloralamide is the least likely to affect the heart, but its action is sometimes considerably delayed, and is never very prompt. Amylene

hydrate is somewhat uncertain, both in the initiation and duration of its effect. The sleep produced by all the members of this group is usually light and refreshing, and closely resembles natural sleep.

IV.—MEDIUM HYPNOTICS.

1. **Paraldehyde,** a polymer of ordinary aldehyde (CH_3CHO), is a colourless fluid, with a characteristic and very unpleasant taste and odour, which it is practically impossible to conceal. Strongly sweetened tea is said to act as well as anything can. In America, paraldehyde is given in iced water or mixed with pounded ice. This conceals the taste, and prevents the burning sensation caused by the irritation of the œsophagus and stomach. It is best given in capsules, but even so the breath will smell of paraldehyde for some time. It is unstable, and must be protected from light, fairly soluble in water, and mixes with spirit in all proportions. The dose is ½ to 2 drachms (about 2 to 8 cc.) It usually produces five to eight hours' sleep, and is prompt and reliable in its operation. While somewhat closely resembling amylene hydrate in its action, it is probably a rather more powerful drug, and occupies an intermediate place between the two groups. Older patients, whose blood-pressure is above normal, are said to require larger doses of paraldehyde in order to produce sleep.

The main advantages possessed by paraldehyde as a hypnotic are that the sleep produced is light and natural, and that undesirable effects on the

heart are very unusual indeed. The principal disadvantages, besides its very unpleasant taste, are that it may produce excitement and a condition resembling intoxication, and that it occasionally causes digestive disturbances and respiratory failure. The latter, however, as also is the case with the cardiac symptoms, only occurs after large doses. Tolerance is rapidly established, and a habit has been known to arise, in spite of the nauseous taste of the drug. A condition similar to delirium tremens is produced. A case is recorded in which 100 gm. (more than 3 oz.) were taken with no ill effects beyond prolonged slumber;* in others, drowsiness and diuresis have been the chief symptoms. Nevertheless, it is certainly inadvisable to give paraldehyde to persons who suffer from any digestive or respiratory disorder.

An interesting case of fatal paraldehyde poisoning has been recorded by Lovell Drage.† The patient, a woman aged 46, was the victim of drug habits. In thirty-three hours she took at least 13 drachms (44 cc.) and on the top of this a single dose of 2 oz. (57 cc.) which proved fatal in about three hours. The symptoms were unconsciousness, cyanosis, intermittent pulse, profuse sweating, and shallow, regular respiration. I have not been able to find another fatal case recorded.

2. **Sulphonal** is a somewhat insoluble crystalline body, possessing neither taste nor odour, and

* Mackenzie, *Brit. Med. Jour.*, 1891, p. 1255.
† *Lancet*, 1900, ii., p. 875.

chemically very stable. It may be given as a powder or in tablets, but the latter method is not advisable. The dose is ·7 to 2 gm. (10 to 30 grains). Where a prompt action is required it should be dissolved with the aid of heat. It is useful in the insomnia of nervous and mental disease, though a somewhat high dosage is required ; but it cannot be relied on when incessant cough, severe pain, or respiratory difficulty is present. Sleep may not be induced for two hours, especially if the tablets are used, and often as much as four hours are required. It is light and natural in character, and should last from five to eight hours. Owing to the retention of the drug in the organism, if a dose is required on the subsequent evening, it should be smaller than the first.

The objections to the use of sulphonal are many, and on the whole are well recognized by the profession. A summary mention of them will therefore be all that is necessary here.

After large doses, toxic symptoms are not at all uncommon ; but even with moderate ones, specially predisposed persons may suffer, especially if old or debilitated, or if the drug is administered continuously for more than two or three weeks. It is not readily excreted, and cumulative action occurs ; the minimal toxic dose, moreover, varies greatly in different individuals, and cannot be predicted in any given case. Campbell* has recorded a recovery after 16·2

* *Lancet*, 1897, i., p. 661.

gm. (250 grains) together with one ounce of chlorodyne, and Morris* one after 15·8 gm. (245 grains); while Bachem states that a still larger dose (100 gm.) has been survived. On the other hand, death has occasionally occurred after the ordinary medicinal dose.

Chronic sulphonal poisoning has taken place when ·5 gm. (8 grains) thrice daily had been administered over a long period, and has proved fatal. The main symptoms in acute and chronic cases are alike: Digestive disturbances, with pain, vomiting, diarrhœa or constipation; mental dulness, headache, faintness, muscular inco-ordination and weakness, coma and delirium; urinary symptoms, among which the most important is hæmatoporphyrinuria, due to destruction of red blood-cells and the breaking up of their pigment. Occasionally the symptoms in chronic cases resemble those of general paresis.

3. **Bromural,** a urea derivative containing about 35 per cent bromine, occurs as a white, crystalline body, with a slightly bitter taste and an odour resembling valerianic acid. It is but slightly soluble in cold water, and is therefore best given as a hot drink, or with spirit, in which it is freely soluble. A single dose may be ·3 to ·6 gm. (5 to 10 grains); sleep follows within thirty minutes, and lasts, if the patient is not disturbed, till the following morning. In cases of severe pain, high fever, or considerable mental excitement, bromural fails to produce sleep,

---

* *Brit. Med. Jour.*, 1909, i., p. 1235.

while in others, where there is a recurrent source of irritation, the patient may wake after four or five hours, and not again fall asleep. Beyond a case in which an irritable rash occurred, and a few cases of headache, no undesirable by-effects have at present been recorded after medicinal doses. Even as large a dose as 6 gm. (90 grains) is, according to Runck, without toxic effect, though, owing probably to the rapid excretion of the drug, the hypnotic action is not proportionally increased.* Children, for the same reason, can take bromural in comparatively large quantities: infants may be given a quarter of a ·3 gm. tablet several times daily, and older children ½ to 1 tablet (=2½ to 5 grains) (Ziehen). No tolerance appears to have been observed, and there is no cumulative action, so that the drug may be given continuously over considerable periods, if desirable.

Of the three drugs comprised in this group, bromural appears to be the most satisfactory. The unpleasant taste of paraldehyde, and the unreliability of sulphonal, render them much less valuable than they would otherwise be, while the excitement sometimes produced by the former, and the toxic symptoms which rather frequently occur after the latter, render them very inferior to a drug which is always sedative, even if not hypnotic, and hardly ever gives rise to any undesirable effects. Bromural has a definite limit to its usefulness, a limit which

* *Münch. med. Woch.*, April 9, 1907.

cannot be extended by increasing the size of the dose; within that limit, however, it appears to be a satisfactory drug, and all that is now required to establish its position is the clinical experience of a few decades.

V.—POWERFUL HYPNOTICS.

1. **Chloral Hydrate,** which may be considered as the standard hypnotic in this group, has now been employed for some forty years, and therefore needs very little consideration in this place. Its value is somewhat unnecessarily minimized by some writers, such as Ziehen,* who think that it should be entirely excluded from our materia medica; on the other hand, it has certain very definite disadvantages, which have probably become more apparent owing to the large number of years during which the drug has been employed, and to the fact that it is not infrequently taken by those who are not under medical care. It is, on the whole, a remarkably reliable drug, and its main disadvantages are its unpleasant taste, its depressant action on the heart and vasomotor centre, and the variability in its toxic dose occasioned by idiosyncrasy. Children take it well.

Eglatol is a mixture of chloral hydrate, phenazone, caffeine, and methyl-urethane. It is a colourless fluid, partially soluble in water, and may be given in capsules in doses of ·5 to 1 gm. (8 to

* *Loc. cit.*

15 grains). The toxic action of both the chloral hydrate and the phenazone are said to be diminished by their combination. It is apparently a mild hypnotic and not very reliable, but the observations on its use are as yet too few for any certain opinion to be given as to its value.

2. **Trional** is a colourless, crystalline powder, not very soluble in water (1–110 parts at body temperature) but easily in alcohol. It should never be given in tablet form, though as a powder it acts fairly well. Hot milk, tea, or water should be given immediately after the powder. The solutions have a bitter taste. The dose is ·6 to 2 gm. (10 to 30 grains), but larger doses have occasionally been given in cases of mental disease. It may also be given as an enema. Children of three can take ·1 gm. (1½ grains), and at ten years ·3 to ·5 gm. (5 to 8 grains) may be administered.

Trional is not such a powerful hypnotic as chloral hydrate, but is more powerful than the closely allied body sulphonal; it also acts more promptly—in half to one hour—and does not cause drowsiness or heaviness on the following day; six to eight hours' sleep is produced. It is fairly reliable in all cases where there is not extreme excitement or delirium, but is not of any use where pain is present. The toxic symptoms, both acute and chronic, are similar to those produced by sulphonal, and the minimum fatal dose is similarly variable; enormous doses of 12 gm. (185 grains) plus 1·3 gm. (20 grains) of veronal have failed to produce more than a deep

and prolonged coma.* Chronic poisoning has occasionally been known to occur with small daily doses (15 to 30 grains), but this is rare. Women are more liable to develop toxic symptoms than men.

A useful combination of hypnotics consists of 15 grains of trional and 30 minims of paraldehyde in an ounce of the mist. amygdalæ B.P. (emulsum amygdalæ U.S.P.). It acts much more rapidly than trional alone, and is generally a far more effective hypnotic (Ziehen).†

3. **Veronal** is a white, crystalline powder, slightly bitter, and possessing no odour. It is only slightly soluble in cold water, but more freely in hot water and dilute alkalies. It should *never* be given in solid form, as its action is then uncertain and delayed, but may be prescribed in hot tea, soup, or gruel. Milk should not be used, as the alkaline salts produce a substance possessing an unpleasant, bitter taste.‡ Sleep is usually induced in fifteen to thirty minutes, and lasts from six to eight hours. The usual dose is ·2 to ·3 gm. (3 to 5 grains), but larger ones are often necessary, especially where there is any considerable mental excitement, when 7 or 8 grains may be necessary. v. Leyden § does not think it advisable to go beyond 1 gm. (15 grains), as toxic symptoms may show themselves with large doses, without any real increase in hypnotic effect. Some drowsiness

---

* Mackintosh, *Lancet*, 1910, i., p. 104.
† *Deut. med. Woch.*, 1908, No. 14.
‡ v. Leyden, *Folia Therap.*, i., 4, p. 114.
§ *Loc cit.*

on the following day may occur with doses as low as 5 grains,* though it is not usually noted unless 15 grains have been taken. The hypnotic strength has been variously estimated; it is at any rate more powerful than trional and bromural, and possibly than isopral. Medicinal doses appear to have no adverse effect on the heart, kidneys, or respiration. The drug is most suitable for the more resistant cases of insomnia, such as those dependent on irritating cough, the delirium of fever or alcoholism, or pain, if not too severe.

Veronal has gained great popularity, both with the profession and with the public, as a safe and efficient hypnotic, and is probably, therefore, prescribed in many cases where a less powerful drug would be safer and equally efficacious. The "safety" of veronal is probably conditioned by three separate factors: (1) It contains no chlorine atoms, which usually denote cardiac depression; (2) Its insoluble character makes its absorption comparatively slow; (3) It is fairly easily eliminated by healthy kidneys, though in renal disease this does not take place; all forms of Bright's disease are therefore a contra-indication for its use.

Fischer and Hoppe,† who experimented with sodium veronal, found that after oral administration traces could be detected in the urine in forty minutes, after rectal administration in thirty minutes, and after subcutaneous administration in fifteen minutes;

* Foxwell, *Ibid.*, i., 3, p. 73.

† *Münch. med. Woch.*, 1909, vol. ii., p. 1429.

in each case the appearance of the drug in the urine corresponded to the onset of the hypnotic effect. Single ½-gm. doses (8 grains) of sodium veronal (=·45 gm. veronal) were excreted in about four days, but the total amount given was not quite quantitatively recovered. In cases where the drug was taken daily, everything seemed to depend on the age of the patient and the integrity of the renal epithelium. A young girl with normal kidneys took ·3 gm. (5 grains) every night for thirteen days, and practically excreted the entire amount during the same period, whereas a man of 41 with unsound kidneys, who took ·5 gm. (8 grains) daily for five days, only excreted ·8 gm. (12 grains).

In other respects, it is no safer, probably, than other hypnotics, and the consequences attending an overdose or its employment in unsuitable cases are very similar to those seen after other drugs. There is some evidence that, like the sulphur-containing hypnotics, veronal sets up toxic symptoms in women more easily than in men. These untoward results may be considered in three main groups: (*a*) Those following small or moderate doses, and commonly said to be the result of special personal idiosyncrasy; (*b*) Those following large or excessive doses; (*c*) Those following repeated doses (veronal habit).

(*a*). Among the slighter and not very infrequent toxic manifestations which may occur after small doses of 3 to 5 or 10 grains are: Prolonged drowsiness (more than twenty-four hours), headache, dizziness, and other unpleasant sensations in the head.

Digestive disturbances may include loss of appetite, constipation, nausea, and vomiting; while cutaneous eruptions of a morbilliform or scarlatiniform character are not uncommon. Urticarial and bullous rashes, extreme pruritus, and œdema of the face have also been observed. Urinary disturbances, such as suppression, hæmaturia, and albuminuria, have been described. More serious symptoms may occur after larger doses, such as disturbances of sight and speech, reeling gait, tetanic convulsions, cyanosis, and collapse; a condition resembling alcoholic intoxication may supervene, or there may be cardiac symptoms, such as præcordial pain and slow pulse.

The condition of the pupils varies in veronal poisoning: some writers describe dilatation and others contraction.

(*b*). Large or excessive doses may be fatal, or may be followed by recovery after severe symptoms such as extreme abdominal pain, great headache and dizziness, prolonged coma or somnolence, suppression of urine, or on the other hand marked diuresis. Severe sweating and pyrexia have also been observed. The size of the fatal dose has varied considerably in the recorded cases. The following table will illustrate this (p. 162).

It will be observed that no case of recovery has been reported where more than 10 gm. (150 grains) of veronal had been taken, and that much smaller doses have given rise to serious symptoms, and sometimes had a fatal issue. The smallest recorded fatal dose appears to be 1 gm. (15 grains), and a

	AUTHOR	REFERENCE	DOSE	RESULT	NOTES
1	Alter ..	q. Seiffert	1 gm. (15 gr.)	Death	
2	—— ..	*Brit. Med. Jour.*, 1909, i., p. 1387	,, ,,	,,	
3 4	Friedel ..	q. Seiffert	3 gm. (45 gr.)	,,	
5	Parsons	*Brit. Med. Jour.*, Sept. 19, 1908	4 gm. (60 gr.)	,,	In divided doses during 48 hours
6	Zörnlaib ..	*Wiener med. Woch.*, 1906, No. 50	6 gm. (90 gr.)	,,	
7	Walker ..	*Lancet*, 1909, i., p. 1558	6·6 gm. (99 gr.)	,,	
8	Bahrdt ..	*Münch. med. Woch.*, 1907, No. 6, p. 293	9 gm. (135 gr.)	,,	Patient had taken 3 gm. (45 gr.) the previous day.
9	,, ..	,, ,, ,,	10 gm. (150 gr.)	,,	
10	Zörnlaib ..	*loc. cit.*	,, ,,	,,	
11	Holzminden case ..	*Münch. med. Woch.*, 1905, No. 47, p. 2269	,, ,,	,,	A mistake in dispensing for a vermifuge.
12	F. Ehrlich ..	*Münch. med. Woch.*, 1906, No. 12, p. 559	10 gm. (165 gr.)	,,	
13	Scheider ..	q. Bachem	,, ,,	,,	
14	Pariser ..	q. Seiffert	,, ,,	,,	
15	F. Ehrlich ..	*loc. cit.*	15 gm. (235 gr.)	,,	
16	Umber ..	*Münch. med. Woch.*, 1906, No. 51, p. 2557	20 gm. (300 gr.)	,,	Patient was also suffering from pneumonia.
17	Embden ..	*Münch. med. Woch.*, 1908, No. 19, p. 1050	,, ,,	,,	Enormous dilatation of heart occurred.
18	Senator ..	q. Harnack, *Münch. med. Woch.*, 1905, No. 47, p. 2269 ..	2 gm. (30 gr.)	Recvry.	Very small, weak, irregular pulse.

19	Neumann ..	*Berl. klin. Woch.*, 1908, No. 38	3·5 gm. (53 gr.)	,,	Glycosuria observed.
20	Nienhaus ..	*Münch. med. Woch.*, 1907, No. 25, p. 1250; *C.-B. f. Schw. Aerzte*, xxxvii., No. 12, 1897	4 gm. (60 gr.)	,,	Uræmic symptoms; ·1 gm. excreted next day; recovery slow (14 days).
21	Gerhartz ..	q. Harnack, *loc. cit.*..	4 gm. (60 gr.)	,,	Almost fatal, through cardiac failure.
22	Umbér ..	*loc. cit.*	4 gm. (60 gr.)	,,	Patient also took ·08 gm. (1⅓ gr.) codeine.
23	Geiringer ..	*Wien. klin. Woch.*, Nov. 23, 1906, p. 1245	4·5 gm. (68 gr.)	,,	
24	Masey & Drappier	q. Harnack, *loc. cit.*..	,, ,,	,,	Severe symptoms, though not fatal.
25	Wild ..	*Münch. med. Woch.*, 1906, No. 25, p. 1231	6 gm. (90 gr.)	,,	
26	Clarke ..	q. Harnack, *loc. cit.* ..	7·5 gm. (113 gr.)	,,	
27	Hoeftmann ..	q. Seiffert, *op. cit.* ..	9 gm. (135 gr.)	,,	
28	Held ..	*Ther. Gaz.*, 1905, p. 676	,, ,,	,,	Stomach washed out within a few hours. Stupor and tetanic convulsions; treatment by baths and cold effusions; recovery in 4 days.
29	Mörchen ..	*Münch. med. Woch.*, 1906, No. 25, p. 1231	8–10 gm. (120-150 gr.) ..	,,	Patient also took 5–6 gm. (75–80 gr.) sulphonal and trional. Not more than $\frac{1}{10}$ of the whole was vomited.
30	Friedländer ..	q. Harnack, *loc. cit.* ..	10 gm. (150 gr.)	,,	Patient also took 6 gm. (80 gr.) trional.

dose of 4 gm. (60 grains) appears to be distinctly dangerous, though not necessarily fatal.

The treatment of acute veronal poisoning consists firstly in removing the poison by the use of emetics, washing out the stomach, and purgatives such as castor oil, or enemata. It should be remembered in this connection, that the drug is often very slowly absorbed, so that even after a considerable time has elapsed these measures may be worth while. After the washing out, tannin solutions may be introduced into the stomach. Stimulants such as hot coffee or camphor injections, and diuretics, may be given, or the patient may be placed in a warm bath and sponged with cold water. Strychnine, digitalin, pilocarpine, and atropine have also been employed as indications arose.

(*c*). Not a few cases have been recorded in which a veronal habit has become established, and toxic symptoms manifested themselves. There is some want of agreement among writers as to the occurrence of a cumulative action, but it appears that this must certainly occur in some cases, especially if there is also present any renal insufficiency or constipation. In Laudenheimer's case, 250 gm. (nearly 9 oz.) were taken by a morphinomaniac in two months. Motor weakness, tremor, speech-disturbances, diminution of urine, and a general condition resembling drunkenness resulted. Steinitz has reported a case in which somewhat similar symptoms occurred in a woman after six months' veronal taking. Somewhat different were the results of ·5 gm. (8 grains)

of veronal taken every night for six months by a mental patient of Dobranschausky's. She suffered from cachexia and anæmia, with considerable amounts of urobilin and hæmatoporphyrin in the urine. A fatal case is reported by Kress after ·5 to 2 gm. (8 to 30 grains) had been taken daily for a year, but it does not appear certain that the drug was entirely responsible for the event. Ollerenshaw reports an interesting case in which the symptoms were headache, optic neuritis, mental aberration, and attacks of muscular spasticity.

Kress has observed drowsiness and loss of appetite after three or four days in some patients to whom ·5 gm. (8 grains) had been administered nightly, which he attributed to a cumulative action.

Sodium Veronal, or **Medinal,** differs from veronal in being easily soluble in water. Its action appears to be similar to that of veronal, and the dosage is the same. The advantage of the solubility is that it may be given as an enema or intramuscularly. Its disadvantages are two : in the first place, the taste is objectionable, and in the second, as veronal owes its relatively safe character largely to the fact that it is insoluble and therefore only absorbed slowly, it would seem that this soluble and easily absorbed drug must be more liable to set up toxic symptoms in cases of idiosyncrasy or where somewhat large doses are given.

4. **Proponal** is a colourless, crystalline body, very insoluble in cold water, but easily soluble in dilute alkalies. Its solutions have a somewhat

bitter taste, and it is even more powerfully hypnotic than veronal, to which it is closely allied chemically. The usual doses are about half those of veronal; ·15 to ·5 gm. (2 to 8 grains) are effective doses, even when pain is present. Sleep is often produced in ten to fifteen minutes, though usually thirty to forty-five minutes must be allowed, and it lasts some seven hours. If necessary, ·3 to ·6 gm. (5 to 10 grains) may be dissolved in ·4 per cent warm sodium bicarbonate solution and given as an enema. The toxic symptoms which have been observed after medicinal doses closely resemble those caused by veronal; among the commonest is a feeling of heaviness lasting over the next day. The heart is occasionally affected, though not usually. Tolerance is somewhat soon established—often in three or four days. The great disadvantage of proponal, and one which in the opinion of many will outweigh any of its advantages, is that the toxic dose is only a very little greater than the effective hypnotic dose. The maximum of ·5 gm. (8 grains) by the mouth should never be exceeded.

5. **Neuronal** is a colourless, crystalline powder, sparingly soluble in cold water, easily soluble in alcohol. It has a faint camphoraceous or aromatic odour, and a bitter taste. It contains 41 per cent of bromine, and is decomposed by alkalies, prussic acid being formed. It must not therefore be prescribed in alkaline mixtures. This decomposition is said not to occur in the animal body after absorption. The dose of neuronal in slighter cases is ·5 to

1 gm. (8 to 15 grains) but in the more severe cases, especially among insane patients, much larger doses, up to 3 gm. (45 grains), may be required. Sleep usually supervenes in twenty to thirty minutes, and lasts seven to eight hours. It is, however, considered a somewhat uncertain hypnotic by some writers.

Though Siebert* is inclined to place neuronal below veronal in hypnotic power, it is usually regarded as one of the strongest narcotic drugs. Ollerenshaw observes that the sleep produced is deep and heavy, suggesting intoxication, and that frequently headaches and drowsiness are present on the following morning. It has, moreover, a general depressant effect, and is thus unsuitable for patients with organic heart lesions. He regards it as more powerful than veronal, but finds its depressant effect on the mental and bodily functions a bar to its general employment. It is unsuitable where pain is present, and in the sleeplessness of phthisical patients, owing to this depressant effect. Digestive disturbances, nausea, abdominal pain, vomiting, and diarrhœa occasionally occur, as well as nervous symptoms, such as numbness, headache, and ataxia. Occasionally the pulse becomes weak and dicrotic, and urticarial rashes have been observed. A case has been recorded† in which death took place after neuronal had been regularly taken for some time, but it does not appear that the drug was

* *Psych. Neurol. Wochenschr.*, 1904, No. 10.

† Weifenbach, *Zentralb. f. Nervenh. u. Psychiatrie*, 1905, No. 182.

responsible for the event. Tolerance, with loss of hypnotic effect, is somewhat rapidly established.

Of the powerful hypnotics contained in this group, chloral hydrate and veronal are the two which have hitherto had the widest application, but it seems doubtful to the present writer whether, in the majority of cases, it would not be better to employ one of the milder hypnotics instead of these potent drugs, which ought to be reserved for cases in which the others are ineffective. By diminishing the dose a slighter effect can, of course, be gained; but apart from all other considerations, it does not appear wise to employ, as a general rule, substances capable of producing such marked effects that self-drugging and chronic intoxications may, in a number of cases, be induced. Chloral hydrate has a peculiarly unenviable reputation in this respect; but then it must be remembered that it has been in use now for forty years, and has become widely known to the public. Veronal has only been employed for an eighth part of that time, but is already a " popular " drug, and has also already produced cases of veronal habit. That both these drugs are most valuable, and have a distinct and important place in our pharmacopœia, is not for a moment denied, but it is certainly worth while to consider in any individual case whether some milder drug would not be equally successful, while not carrying with it the chances of habit formation or the development of undesirable bye-effects.

Pain, delirium, excitement, or the failure of a less powerful drug, may be taken as indicating the necessity for one of the bodies contained in this group. Probably, in view of its many advantages, veronal will be selected. But it must never be forgotten that toxic symptoms, sometimes severe and occasionally fatal, may be produced by this "safe" hypnotic, and under no circumstances should patients be instructed to buy a bottle of tablets for themselves, to be taken according to their own inclination, and possibly in doses which no rational physician would dream of prescribing.

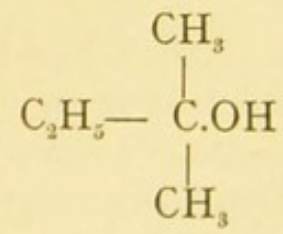
Appendix to Chapter V.

In the following table are placed the more important hypnotics, arranged according to their chemical structure, and grouped in the manner suggested by Fraenkel.

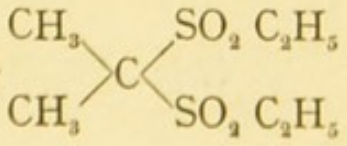
1. **The Alcohol Group,** containing ethyl alcohol and other bodies, the physiological action depending on the alkyl group.

(*a*) Ethyl alcohol $CH_3.CH_2.OH$.

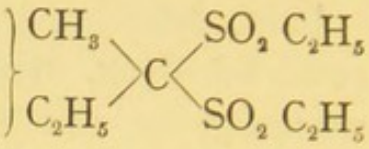
Amylene hydrate (tertiary amyl alcohol)



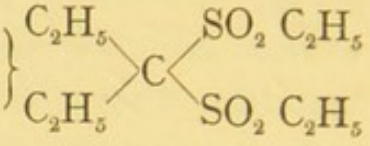
(*b*) Sulphonal (dimethyl-diethyl sulphone)



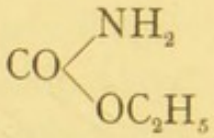
Trional (methyl-ethyl-diethyl sulphone)



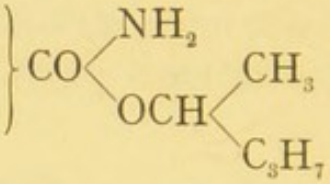
Tetronal (diethyl-diethyl sulphone)



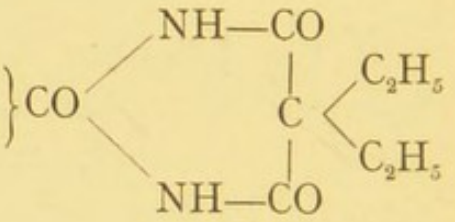
(*c*) Urethane



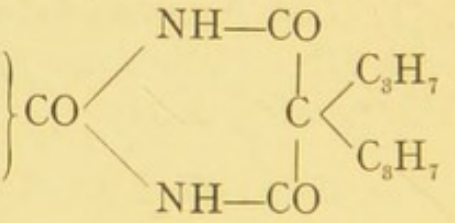
Hedonal (methyl-propyl-carbinol-urethane)



Veronal (diethyl-malonyl-urea)

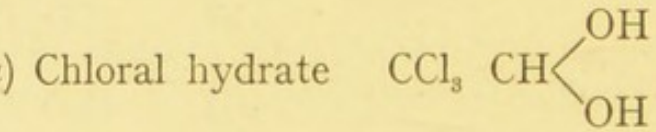


Proponal (dipropyl-malonyl-urea)



2. **The Chloral Group,** containing chloral and other bodies in which the halogen determines the hypnotic action. In this group might also be included the volatile anæsthetics such as chloroform.

(*a*) Chloral hydrate



Chloralose $C_6H_{10}O_5.CCl_3CHO$.

Chloralamide (chloral-formamide) $CCl_3CH(OH)(NH.OCH)$

Isopral (trichlor-isopropyl-alcohol) $CCl_3.CHOH.CH_3$

Chloral urethane $CCl_3CH(OH)(NH.COOC_2H_5)$

(*b*) Bromal CBr_3CHO

Neuronal (diethyl-brom-acetamide) $(C_2H_5)(C_2H)CBr.CONH_2$

Bromural (monobrom-iso-valeryl-urea) $(CH_3)(CH_3)CH.CHBr.CONH.CONH_2$

3. **The Paraldehyde Group,** in which the aldehyde or ketone radicle produces the hypnotic action.

Paraldehyde $(CH_3CHO)x$

Propion (diethyl ketone) $C_2H_5.CO.C_2H_5$

Hypnone (acetophenone) $C_6H_5.CO.CH_3$

CHAPTER VI.

ANÆSTHETIC DRUGS: — (I.) Direct Local Anæsthetics; (II.) Spinal Analgesics, or Indirect Local Anæsthetics; (III.) General Analgesics and Amnesics.

ANÆSTHETICS.

IT is hardly possible scientifically to draw a hard and fast line between the two groups of drugs known as hypnotics and general anæsthetics. The main differences to be observed are in the physical rather than the chemical characters of the substances concerned, and it is on these that their physiological behaviour and their practical applications may be said to depend. Both owe their activity to their power of influencing chemically the higher cerebral cells; the general anæsthetics, being very volatile bodies, are rapidly absorbed and excreted almost at once, so that their effect only lasts during their continuous administration; the hypnotics, on the other hand, being more stable liquid or solid bodies, can be given in a single dose, the physiological effects of which will begin some time after the administration, and will continue so long as a sufficiency of the drug remains unexcreted.

Although the subject of general anæsthesia by means of chloroform and similar substances has been largely investigated and re-investigated of late

years, there have been no new drugs introduced of sufficient importance to require special notice in a work like the present. This chapter, therefore will be devoted to the consideration of those drugs which are capable of producing anæsthesia by other means than inhalation. Various methods have been devised for their employment, and their action may be directed upon any part of the nervous system, central or peripheral. To avoid needless repetitions, some account will first be given of the various drugs, with their usual doses; and then the different modes of administration will be discussed in detail, according to the following scheme :—

I. *Direct local anæsthesia:* (1) By hypodermic injection; (2) By intravenous injection; (3) By application to mucous surfaces, especially the conjunctiva.

II. *Spinal analgesia, or indirect local anæsthesia.*

III. *General analgesia and amnesia by hypodermic injection.**

A.—DRUGS.

Cocaine.—The oldest and most widely employed of all the "local anæsthetics" is the alkaloid derived from the *Erythroxylon coca.* The chemical constitution of this substance has been accurately known for some time, and though two synthetic bodies have been constructed and successfully

* The terms "direct" and "indirect" are here applied in the sense indicated in the context, and not in the sense in which they are used by Bier in describing his intravenous method (*vide* p. 184).

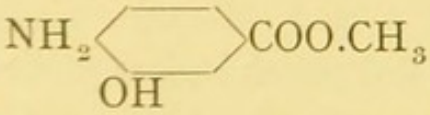
applied in practice, which are of a closely similar chemical type, yet the majority of the newer "local anæsthetics" differ widely from their physiological prototype. Indeed, the function of numbing the peripheral sensory nerves or their endings is common to very many members of the great aromatic series of carbon compounds, one of the simplest, from a structural point of view, exhibiting this action to a remarkable extent. Phenol  OH, or oxy-benzene, has long been used as a local anæsthetic, especially for allaying the pain of a carious tooth, and between this and the complex derivatives recently introduced, there are a large number of bodies which in their structure bear but little resemblance to each other. These will be dealt with in the following order: Eucaine *α* and *β*, orthoform, orthoform *neu*, nirvanine, anæsthesin, novocaine, holocaine, acoine, stovaine, alypin, tropacocaine, and scopolamine.

α- and *β*- **Eucaine.**—These bodies, which closely resemble the natural alkaloid cocaine in their chemical constitution, are colourless crystals, the former soluble in 10 parts of water and the latter in 30. The former has been practically abandoned in practice owing to its irritant action on the tissues, and the latter is mainly employed in the form of a salt, usually the lactate.

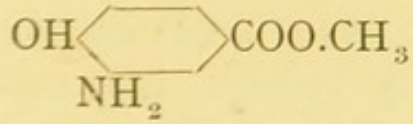
β-Eucaine is less toxic than *α*-eucaine (1 : 4), and its anæsthetic action is, weight for weight, about equal to that of cocaine. It may be sterilized by boiling,

and its vasodilator action checked by admixture with adrenin solution. A 10 per cent solution of the lactate gives rise to swelling, thickening, and sloughing of the skin when injected. For ophthalmic and dental work, a 2 to 3 per cent solution of the lactate of β-eucaine may be employed; for infiltration anæsthesia ·12 per cent, for regional anæsthesia 2 to 5 per cent; and for throat, nose, and ear work 10 to 15 per cent. The diluent should be sterile physiological salt solution (·7 per cent). If adrenin is used, 2 to 5 drops of a 1 per thousand solution may be added to each 100 cc. ($3\frac{1}{2}$ oz.).

Orthoform and **New Orthoform** are isomeric bodies, derived from oxyamidobenzoic acid, and are but slightly toxic.



orthoform



orthoform *neu*

The second form is cheaper than the old, and equally active, but neither of them is capable of acting through the unbroken skin or mucous membrane. Both forms are somewhat insoluble and very hygroscopic, and their salts (such as the hydrochloride) though soluble, are irritant. Orthoform may be used in the form of a 10 per cent ointment or dusting powder, or a 25 per cent emulsion may be applied. The hydrochloride is too irritant and the base too insoluble for hypodermic use.

Internally, it is given in doses of from ·2 to ·5 gm. (3 to 8 grains) several times daily, in hyperæsthesia of the gastric mucosa. Suppositories for painful hæmorrhoids may contain ·2 to ·5 gm (3 to 8 grains) in cocoa butter.

Nirvanine is a diethylglycocoll derivative of orthoform, and is still less toxic. It is very soluble, has no action on unbroken skin, and can be sterilized by boiling. Its anæsthetic power, weight for weight, is less than that of cocaine. It is, moreover, irritant and liable to set up painful local œdema. It has been employed in 2·5 per cent solution for infiltration anæsthesia, and in 5 per cent solution for ophthalmic work.

Anæsthesin is a derivative of *para*-amidobenzoic acid ($NH_2.C_6H_4.COOH$), and closely resembles orthoform in its physical and physiological properties. It is usually employed as a 5 to 10 per cent ointment or dusting powder. It differs from orthoform in being capable of acting through the unbroken mucous membrane (Lipowski).

Novocaine is one of the most important of modern analgesics. It is the hydrochloride of a derivative of *para*-amidobenzoic acid, and consists of colourless needles, soluble in their own weight of water. The solutions are stable, can be sterilized by boiling, are non-irritant, and keep well. Its toxicity is slight, and its anæsthetic power, weight for weight, equal to that of cocaine. The anæsthesia produced is complete but somewhat transient, and its duration may be increased by the addition of some adrenin

solution (*v.i.* p. 189). For infiltration anæsthesia ·25 to 2·0 per cent solutions may be employed, and as much as ·3 to ·4 gm. (4 to 6 grains) may be injected. ·15 gm. (2 grains) will produce fifteen minutes' anæsthesia. About five minutes' interval after the injection should be allowed before the operation is begun. It does not cause local hyperæmia. For mucous membranes, a 10 per cent solution is used, and for spinal analgesia, a 4 to 5 per cent solution, of which as much as 2 or 3 cc. (35 to 50 min.) may be injected.

Holocaine, which is a condensation product of phenetidin and phenacetin, is used in the form of its hydrochloride. This substance consists of a white, crystalline powder soluble in 45 parts of water. The solutions keep well, and produce rapid anæsthesia, but the drug is much more toxic than cocaine. A 1 to 3 per cent solution is employed. It is not very suitable for ophthalmic work, as it is somewhat irritating to the conjunctiva. Two or three drops of a 1 per cent solution will produce anæsthesia within one minute, and two or three instillations at five-minute intervals will prolong the condition for about forty minutes.

Acoine is the hydrochloride of a guanidine derivative, the chemical structure of which is somewhat complicated. It is a colourless, crystalline powder, slightly soluble in water, less toxic than cocaine, and more prompt and enduring in its action. It is, however, irritant; its solutions are decomposed by light, and are acted on by alkalies present

in glass. 1 per cent in normal saline is a suitable strength for the solution.

Stovaine.—This and the next compound are nitrogen derivatives of the ester of tertiary amyl alcohol and benzoic acid. Stovaine hydrochloride is a white, hygroscopic, crystalline powder, very soluble in water; the solutions are stable, and may be sterilized by boiling. It is generally considered a more powerful anæsthetic, weight for weight, than cocaine, and it is certainly less toxic. In dogs it is said to be three times less toxic when given intravenously, though by the hypodermic way, the difference is less marked (Baylac). Its vasodilator action is slight, and may be checked by adding to it a little adrenin solution. For local anæsthesia ·5 to 1 per cent solutions are used; for the conjunctiva 2 per cent; for nose and throat work 10 per cent; for spinal anæsthesia ·01 to ·1 gm. ($\frac{1}{4}$ to $1\frac{1}{2}$ grain), not more than 1 cc. (17 minims) being injected at a time. For local anæsthesia the maximum should be ·12 gm. ($1\frac{3}{4}$ grain), which will produce twenty minutes' anæsthesia; further amounts will prolong the condition if necessary; the anæsthesia begins immediately. Strong solutions are irritant; 5 to 10 per cent sets up gangrene and sloughing at the site of injection.

Under the trade name **Andolin** is sold a mixture of anæsthetics for spinal analgesia, which is composed of

β-Eucaine	·5	Adrenin hydrochloride	·008
Stovaine	·75	Physiological saline solution	ad 100

Alypin (hydrochloride) consists of small, colourless crystals, easily soluble in water. The solutions are not acid, can be sterilized by boiling, and are only slightly irritant. The toxicity of alypin is generally considered to be less than that of cocaine, and its anæsthetic power, weight for weight, at least equal. It is a slight vasodilator, and has no action on the pupil. In ophthalmic cases a 2 per cent solution is used, for the urethra and bladder a 1 to 2 per cent, and for all other mucous membranes a 10 per cent. Ten drops of a 10 per cent may be given internally for gastric pain of various kinds. 1 to 2 per cent solutions act well for infiltration. Suppositories containing ·01 to ·02 gm. ($\frac{1}{6}$ to $\frac{1}{3}$ grain) may be used to produce anæsthesia of the rectum.

Tropacocaine is a natural alkaloid occurring in the leaves of Java coca, which forms a sort of link between cocaine and atropine. It is chemically an ester of a body called pseudotropine, which is isomeric with ordinary tropine.* Tropacocaine is less toxic than cocaine, but it produces more intense and rapid anæsthesia. Its solutions are stable, and can be kept for a month without decomposition. It produces no dilatation of the pupil. The hydrochloride is the salt usually employed, and consists of white, soluble crystals. The usual strength for solutions is 4 to 5 per cent, to which ·6 per cent

* Pseudotropine was formerly the name given to another substance, produced by the decomposition of hyoscine or scopolamine. This body is now known as oscine.

sodium chloride may be added. For spinal anæsthesia ·075 gm. (1¼ gr.) is the usual dose.

Scopolamine, the hydrobromide of which is used hypodermically as an anæsthetic, is a natural alkaloid allied to atropine, and has been also named hyoscine. Its constitutional formula is unknown. The natural alkaloid is lævorotary; a racemic variety is known as atroscine. These varieties all act in the same way on the central nervous system.

Scopolamine differs from atropine mainly in acting more powerfully, rapidly, and transiently on the peripheral nerve-endings, and in depressing the central nervous system much more strongly; the medullary centres are depressed, blood-pressure falls, respiration is slowed, and there is no stimulant action whatever. It is rapidly broken down and excreted, which renders it comparatively safe; but some persons are extraordinarily susceptible, and ·00065 gm. ($\frac{1}{100}$ gr.), the usual dose by the mouth, has been fatal. Pilocarpine or caffeine should be given subcutaneously in cases of scopolamine poisoning. Excitement and convulsions, which are sometimes observed, are said to be due to an impurity, *apoatropine*, which may be detected by the following method*: A drop of potassium permanganate solution is added to the solution to be tested. If scopolamine or atropine only are present, no change occurs. If apoatropine is present, in as small an amount as 1–20,000, a brownish-

* Kessel, *Arch. Internat. de Pharm. et de Thér.*, xvi., p. 1, 1906.

yellow colour is produced by the formation of oxide of manganese.

B.—METHODS OF ADMINISTRATION.

I.—DIRECT LOCAL ANÆSTHETICS.

1. **By Hypodermic Injections.**—In the year 1905 Professor Braun* laid down certain criteria, which have been generally accepted, for the determination of the suitability of any new substance for producing local anæsthesia :—

(*a*). It must, in proportion to its anæsthetizing power, be less toxic than cocaine.

(*b*). It must not have any irritant action on the tissues or produce any local damage.

(*c*). It must be sufficiently soluble in water ; stable ; and, if possible, capable of sterilization by heat.

(*d*). It must be possible to use it with adrenin solution.

(*e*). It should be rapidly and completely absorbed by a mucous membrane.

Comparative tests were instituted by Braun himself, Baylac,† and Le Brocq,‡ the last named making a very exhaustive research. The only difficulty in accepting the experimental results lies in the fact that the toxicity of drugs varies for different animals, so that determinations of the minimum toxic dose for rabbits may not be a trustworthy guide as to relative toxicities for the human subject.

---

* *Deut. med. Woch.*, Oct., 1905.
† *Prov. Méd.*, June, 1906.
‡ *Brit. Med. Jour.*, 1909, i., p. 783.

The substances which are too insoluble to form good substitutes for cocaine are acoine, holocaine hydrochloride, anæsthesin, orthoform, orthoform *neu*, and β-eucaine. The lactate of the last-mentioned drug is, however, freely soluble.

As regards toxicity, Le Brocq gives the following table, taking cocaine as unity :—

Alypin	1·25	Tropacocaine	0·5
Cocaine	1·0	Novocaine	0·49
Nirvanine	0·714	β-Eucaine lactate	0·414
Stovaine	0·625		

Alypin is thus excluded by its higher toxicity. With regard to stovaine and novocaine, Le Brocq's results are in general accordance with those of Reynier,* who, however, considers novocaine somewhat less toxic and stovaine somewhat more so, than is shown in the above table. Baylac, on the other hand, working with dogs, found stovaine slightly less toxic than cocaine, when injected hypodermically. Braun's results (rabbits) give the same minimal lethal dose for novocaine, but place the toxicity of stovaine considerably higher.

Alypin is discarded by Le Brocq on account of its general toxicity, though the makers state that this is only applicable to rabbits and not to other animals such as dogs. A more serious objection is that raised to it by Braun, namely that it produces irritation and damage to the tissues. Stutzin† who reports favourably on alypin, had two cases of severe necrosis

* *Rev. de Thérap. Med.-Chir.*, Nov. 1907.

† *Deut. med. Presse*, No. 18, 1906.

out of ninety-six applications; but he is doubtful whether these should be referred to the action of the drug or to that of adrenin, which was also employed.

Nirvanine is inferior to the other drugs as a local anæsthetic, and is therefore excluded.

The local effects of stovaine, cocaine, β-eucaine lactate, tropacocaine, and novocaine have been compared by Le Brocq, who finds that in 10 per cent solution they all cause local sloughing except cocaine and novocaine. Of these two the former produces some transient irritation, so that he considers the latter on the whole the best local anæsthetic. Braun found that 5 per cent solutions of stovaine produced gangrene. Danielsen* also considers novocaine less toxic than cocaine and stovaine, and states that he has not found it damage the tissues. He used 1 to 2 per cent solutions for injection, and 10 per cent for spraying mucous surfaces. In sixty operations there were only three unsuccessful. He quotes Braun and Hainecke, and Läwen, who reported on 255 cases with very similar results. Dietze† reported on 120 cases in which novocaine and adrenin were used to produce local anæsthesia; ·125 gm. novocaine and ·00016 gm. boric suprarenin (Höchst) were employed, dissolved in ·9 per cent sodium chloride solution. The strength used was ·5 to 1 per cent. The results were uniformly good.

Schiff, using very dilute solutions (·5 per cent to

* *Münch. med. Woch.*, lii., 46, 1905, p. 2218.
† *Ibid.*, liii., 1906, p. 2429.

·75 per cent) of stovaine, had very good results in 92·5 per cent, and not very good results in 7·5 per cent of the cases, which totalled 196.

2. **By Intravenous Injections.**—Bier, to whom so many of the newer methods of treatment are due, has recently introduced what he calls vein anæsthesia, for want of a better and more accurate term. This method he has employed in 134 cases,* but naturally this small number can only form the basis for further clinical trial. The method consists in rendering the limb, or portion of it to be attacked, completely anæmic by means of constricting bandages, and then injecting directly into a vein 80 to 100 cc. of a ·5 per cent solution of novocaine in physiological salt solution. The injection has to be made under considerable pressure, and is towards the periphery. The anæsthesia is said to be very complete, but disappears rapidly after the upper constricting bandage is removed, thus rendering the suturing of the wound somewhat difficult. Before the operation is concluded, the vein is washed out with normal saline to remove all traces of the anæsthetic which may remain. No general toxic symptoms of any importance have occurred in the limited number of cases observed.

3. **Application to Mucous Surfaces.**—All the drugs which have been discussed in relation to hypodermic anæsthesia have also been employed for spraying the throat or nose, or other mucous membranes,

---

* *Berl. klin Woch.*, 1909, vol. i. ; *Brit. Med. Jour.*, Sept. 18, 1909.

before therapeutic or diagnostic operations. In general, little need be said; the strength of the solution used is usually much greater than that employed hypodermically, and will be found noted in each case under the description of the drug in the earlier part of this chapter. Joseph and Kraus* use a 1 to 4 per cent solution of alypin for washing out the bladder; Renard† uses 8 to 10 cc. (2 to 3 drachms, roughly) of the former strength before applying silver nitrate.

For producing anæsthesia in ophthalmic work, α-eucaine, nirvanine, acoine, and stovaine are far too irritant, while orthoform, orthoform *neu*, and anæsthesin are insoluble. The hydrochloride of orthoform *neu*, though soluble, is also too irritant. Wintersteiner,‡ in an elaborate critical review of the modern local anæsthetics as applied to the eye, points out the disadvantages of cocaine as a kind of standard whereto the others may be compared. These disadvantages are: (*a*) Its general toxicity; (*b*) Its inapplicability to inflamed tissues; (*c*) Its action on the pupil (mydriasis) and the ciliary muscle (paralysis of accommodation); (*d*) Its tendency to damage the corneal epithelium; (*e*) Its action on intra-ocular tension; (*f*) The difficulty of sterilizing its solutions.

As to the various substitutes for cocaine, their properties may be summarized as follows:—

---

* *Deut. med. Woch.*, xxxi., 1905.
† *Gaz. méd. Belge*, 1908, No. 17.
‡ *Wien. klin. Woch.*, xix., 1906, p. 1339.

(i.) *Tropacocaine.*—Though less toxic than cocaine, it has to be used in doses twice as large, so that this advantage is hardly a practical one. The action on the pupil and accommodation is usually absent, but is of little importance. The anæsthesia produced is less complete and more transient than that of cocaine. It is not completely innocuous to the corneal epithelium, and is apt to cause severe irritation, even when dissolved in saline solution, which somewhat mitigates its irritant action. On the whole, it is no advance upon cocaine.

(ii.) *Holocaine.*—This has been praised by many writers; two or three drops of a 1 per cent solution produce anæsthesia in one minute, and two or three instillations at intervals of five minutes, produce an anæsthesia lasting forty minutes. It does not influence the pupil, accommodation, or the intra-ocular tension; its solutions can be boiled, and are antiseptic. It may, however, cause marked irritation and damage to the corneal epithelium, and is more toxic than cocaine.

(iii.) *β-Eucaine lactate*, which is sufficiently soluble and does not affect the pupil, ciliary muscle, or intra-ocular tension, is, even in 2 per cent solution, frequently too irritant. The anæsthesia is rapid and transient, the general toxicity lower than that of cocaine.

(iv.) *Novocaine* is more likely to cause corneal lesions than cocaine, and uveal irritation if injected into the anterior chamber. It is not mydriatic, but its anæsthetic action is slighter and more transient than that of cocaine.

(v.) *Alypin* causes considerable hyperæmia, which is not entirely counteracted by adrenin.* It is a rapid and powerful anæsthetic, and has no action on iris or ciliary muscle. Köllner† says that one drop of a 5 per cent solution will produce corneal anæsthesia, and though it is more active than cocaine in the same dilution, it cannot quite replace it. Neustätter‡ finds that even a 10 per cent solution often fails to render the conjunctiva insensitive. He considers a 5 per cent solution of alypin as painful as a 10 per cent solution of cocaine, and less powerful as an anæsthetic. Less than a 2 per cent solution is quite useless. Beyer,§ however, has not noticed any severe irritation even with strong solutions, and recommends 2 to 5 per cent as a reliable, safe, and rapid analgesic for operations on the cornea, iris, lens, and even bulb.

II.—SPINAL ANALGESIA.

The possibility of producing anæsthesia by injecting drugs into the spinal canal was first suggested by Corning, as the result of some experiments on animals in 1885, but it is to Bier and Hildebrandt that the introduction of a practical method for surgical anæsthesia is due. These observers experimented on themselves with cocaine in 1898, and after some unpleasing personal experiences, they adapted the

* Herford, *Charité Ann.*, xxxi., 1907, p. 595.
† *Berl. klin. Woch.*, xliii., 1905.
‡ *Münch. med. Woch.*, lii., 1905, p. 2015.
§ *Aerztl. Reform. Zeitung*, 17, 1906.

method sufficiently to practical needs to be able to report on 1,200 cases in 1901. Bier, however, advised that cocaine should be abandoned as being too toxic. Various substances were then added to the cocaine solution to render it less diffusible, and in 1904 Bier and Dönitz* reported good results with cocaine and adrenin in 109 cases; Martin employed a similar mixture in 30 puerperal cases,† and reported favourably, while Klopp,‡ as the result of animal experiments, suggested that cocaine solutions might be safely employed when thickened with oil or gelatin. He experimented on dogs, which are very insensitive to cocaine, and moreover have much less cerebro-spinal fluid than man. However, the cocaine was still found to be too toxic to admit of very general use, and it was only the discovery of stovaine by Fourneau in 1904, and its adoption for purposes of spinal analgesia, that prevented that method from being entirely abandoned by surgeons. Since then numerous papers have appeared, most of them in Continental journals, though in this country careful work has been done, amongst others, by Mr. A. E. Barker at University College Hospital, and Mr. Laurie McGavin at the Seamen's Hospital, Greenwich. The drugs mainly used have been :—

Stovaine, ·04 to ·06 gm. in 5 to 10 per cent solution.

Novocaine, ·05 to ·08 gm. in 5 to 10 per cent solution.

---

* *Münch. med. Woch.*, li., No. 14, 1904.

† *Ibid.*, No. 41.

‡ *Arch. f. klin. Chir.*, lxxv., 1, p. 151, 1904.

Tropacocaine, ·05 to ·06 gm. in 5 to 10 per cent solution.

Alypin, ·05 gm. in 5 per cent solution.

Novocaine and cocaine.

Stovaine $\frac{3}{4}$, and cocaine $\frac{1}{4}$, 2 per cent solution, 4 cc. injected twice.

Stovaine ·03 gm. and strychnine ·0005 gm.

To any of these may be added 1 drop of 1 per cent adrenin solution to 10 cc. of the injection.

Biberfeld* who has carried out some experiments to determine generally the toxicity of adrenin solutions (and more particularly the synthetic variety), found that in animals this drug was ten times more toxic when injected into the spinal canal than when injected subcutaneously. Calculated from the results of these experiments. the amount to be injected in man would be from ·05 to ·075 mgm. This closely approximates to the amount contained in 1 cc. of a mixture made up as directed above. However, Biberfeld, found that natural adrenin is much more toxic than the synthetic variety with which he experimented, so that possibly even this small amount must be considered too large a dose. He is inclined to attribute the paralysis and other untoward after-effects of spinal injections to the adrenin rather than to the anæsthetic drug.

Some surgeons withdraw a few cc. of cerebrospinal fluid, and inject the drug dissolved therein ; others, after the withdrawal, inject normal salt solution

---

* *Deut. med. Woch.*, April, 1907.

(·75 per cent sodium chloride) as a vehicle. The injection is usually made in the 3rd or 4th intervertebral space in the lumbar region, the patient being in the sitting position. After a few minutes, the patient is gently and slowly lowered into the recumbent position, the head and shoulders being raised on a pillow. Some surgeons place the patient in the Trendelenburg position in order to diffuse the drug along the spinal canal, and many raise the pelvis on a pillow for the same purpose. In all cases the manipulations must be gentle and slow. Scopolamine-morphine is often employed previously to operation (*vide* p. 195).

Ionnescu*, who employs stovaine and strychnine, injects his solution in the dorsal or even the cervical region, according to the area in which he desires to produce anæsthesia. Milward,† who has recently published a fatal case with autopsy, is of opinion that, even apart from idiosyncrasy, this method is distinctly dangerous except with very moderate doses, and that ·05 gm. is the maximum amount of stovaine which can be used without risk. In his own case, twice that amount was employed, and proved fatal by bulbar paralysis in fifteen minutes.

Krönig and Gauss‡ have shown that the specific gravity of the fluid introduced into the spinal canal influences its diffusion ; thus they found that a light substance, such as stovaine, rises spontaneously to

* *Brit. Med. Jour.*, 1909, ii., p. 1396.
† *Ibid.*, 1910, i., p. 743.
‡ *Münch. med. Woch.*, liv., p. 1969, 1907.

the upper levels of the cord in five to ten minutes when the patient is kept in the sitting position. A heavy body, such as a 10 per cent solution of tropacocaine, on the other hand, does not rise above the site of injection in the lumbar region ; the former substance, therefore, is more suited for abdominal sections, and the latter for operations on the rectum or perineum. If it is desired, the specific gravity of a stovaine solution may be increased by the addition of sodium chloride to the solution. They do not consider that, after the patient has been placed horizontally, the pelvis should be raised to a greater angle than 30°.

A consideration of 12,292 cases from the literature leads to the following conclusions :—

Deaths.—28 deaths are recorded, which amounts to a little over ·2 per cent ; at least six of these were not due to the anæsthetic ; in three others the part played by the anæsthetic was doubtful, in one case death was due to faulty technique, and in another to sepsis.

Severe collapse during the operation is not common, but occasionally occurs. In the cases reported in detail, it occurred in ·26 per cent, not including those in which it proved fatal.

Nerve paralysis.—This sequela usually appears during the second or third week after the operation. Occasionally it is transient, but generally it persists for a fortnight or so, sometimes for as long as six weeks. It may affect one side or both, and may be accompanied by paralysis of the oculomotor nerve.

Paraplegia, hemiplegia, and various pareses have also been observed. A fairly large number of cases of abducens paralysis has been recorded, but it is difficult to estimate its actual frequency. It appears to occur in at least 1 out of 500 cases, and some authors have noted it much more frequently (1 or 2 per cent).

Vomiting and headache are not at all uncommon, either during the operation or afterwards. The headache is sometimes severe, and in the post-analgesic cases, persistent. A case is recorded in which it lasted six weeks (Deetz). About half the cases are affected. Vomiting during the continuance of the analgesia is thought by Himmelheber* to cause a diffusion of the drug into the higher parts of the cord, and so to be a source of danger to the patient.

Pyrexia is occasionally noted after spinal analgesia. Schwarz† recorded it four times in 300 cases. Most authors who mention this phenomenon, describe it as slight and infrequent, but McGavin considers it usual.

Incontinence.—This is exceedingly common during the analgesia. It is rare as a sequel.

Slow pulse is sometimes noted with stovaine injections.

Excitement is rare. Goldschwendt,‡ who noted it, only encountered three in a thousand cases, and attributed it to faulty technique, whereby the drug was accidentally injected into a vein.

---

* *Med. Klin.*, iii., 21, 1907.

† *Wien. klin. Woch.*, xix., 1906, p. 915.

‡ *Ibid.*, xx., p. 1098, 1907.

Nephritis.—This is not a common sequela, and, moreover, is usually slight and transient.

Contraindications. — The majority of observers agree that septic cases, old people (over 60), and children (under 14), those who are timid, nervous, and excitable are not fit subjects for lumbar anæsthesia ; some, however, find children very suitable subjects. Divergent opinions are held as to the influence of diabetes and cachectic conditions. Arteriosclerosis and cardiac weakness are held to be contraindications by some writers. Syphilis (severe or untreated), chronic disease of the central nervous system (such as tabes dorsalis), and pyrexial conditions of unknown causation are included in Bier's list. For purely mechanical reasons, cases of severe scoliosis and very fat persons are unsuited to the procedure.

Failures. — In long-continued operations, and during the lumbar puncture in very nervous persons, a little chloroform or ether is sometimes required ; but apart from this, the cases in which recourse to a general anæsthetic is necessary are infrequent, and, moreover, are indirectly proportional to the skill and experience of the surgeon. Most writers who deal with this point, state that, while at first failures and partial failures were not very uncommon, they have hardly ever experienced them since their technique has been perfected by long practice.

Choice of a Drug.—The drug which has been most frequently employed has in the past been stovaine,

but at present there seems a tendency to regard tropacocaine as the best.* Baisch considers that it is less likely to produce headache and vomiting, while the paralysis of the legs is more complete,† while Wossidlo‡ finds that though recognizable changes in Nissl's granules in the ganglion cells do occur with this drug, they last for so short a time that they can hardly be considered pathological. Novocaine is also recommended, owing to its small toxicity and to the fact that it appears to damage nerve trunks but little. Alypin, though found satisfactory by some, is not generally considered suitable for spinal analgesia. The addition of adrenalin is now usually thought to be a mistake.§ The sequelæ and complications which have already been described, have occurred after all the drugs which have been employed, and there is little statistical evidence as to their relative frequency in each case.

From the experimental side Läwen|| has compared the effects of isotonic solutions of cocaine, novocaine, alypin, and stovaine on the sciatic nerve of the frog. The maximal toxic effect of the first three was seen in one hour, and the excitability of the nerve was diminished by rather less than one-half.

---

* A summary of the general advantages of tropacocaine which reflects the opinion of most authors and experimentalists is given in the *British Medical Journal* of Jan. 15, 1910, p. 157.

† *Beitr. z. klin. Chirurg.*, lii., 1, 1906.

‡ *Arch. f. klin. Chir.*, lxxxvi., 4, 1908.

§ Michelsson, *Münch. med. Woch.*, liv., 50, 1907.

|| *Arch. f. Exp. Path. u. Pharm.*, lvi., 1 & 2, p. 138, 1906.

These three drugs—and novocaine especially easily—could always be washed out by neutral fluids, with complete restoration of excitability. In the case of stovaine, however, this was not possible, and there resulted organic changes in the nerve owing to the acid reaction of the solution. In the cerebrospinal fluid, however, the acidity is neutralized; were it not so, cases of paralysis would be much more frequent. Läwen is careful to point out that these results cannot be applied to man without further experiments. He considers that the superiority of novocaine, stovaine, and alypin, over cocaine is merely due to the fact that they can be injected safely in stronger solution.

III.—GENERAL ANALGESIA AND AMNESIA.

The hypodermic injection of a mixture of scopolamine and morphine produces in many persons a condition which has been termed "twilight sleep" (dämmerschlaf), in which there is much drowsiness, more or less complete insensitiveness to pain, and inability to recollect current events, so that on passing out of the condition, the patient remembers nothing of what occurred during its continuance. The patient is not unconscious or comatose, voluntary movements are not completely abolished, and he can easily be roused; in fact he is specially sensitive to bright lights or sudden noises. The pupils are dilated. Scopolamine and morphine have been employed in three different classes of case: (1) In maniacal or delirious persons as a sedative; (2) As

a preliminary to general inhalation anæsthesia or to spinal analgesia ; (3) In parturition.

1. Scopolamine, with or without morphine, has long been employed in asylum practice in doses of ·0009 to ·003 gm. ($\frac{1}{1\,5}$ to $\frac{1}{2\,0}$ grain). Sleep is usually produced, and sometimes anorexia and vomiting subsequently. Most authors consider it useless and dangerous in alcoholic delirium.

2. As a preliminary measure to general anæsthesia, injections of scopolamine-morphine have been recommended for two reasons : first of all, this procedure renders it unnecessary to use more than very small quantities of chloroform or ether, and secondly, if lumbar analgesia is to be employed, it obviates the distressing nervousness which is displayed by some patients during the operative manipulations. It also diminishes the bronchial secretion, and is thus of some advantage in cases where this is in excess. The contraindications are usually thought to be similar to those for the third group, and, moreover, many authorities consider children unsuited to scopolamine-morphine. Durand,* however, states that children between four and fifteen bear the drugs better than adults. He gives on an average ·5 cc. of a solution containing ·0001 gm. scopolamine-hydrobromide and ·01 morphine hydrochloride per cubic centimetre, but as much as 1 cc. may be given. Chloroform is administered 1½ hours afterwards. Very small amounts are required, and the

* *Thèse de Paris*, 1907.

patients take it very quietly; there is no post-anæsthetic vomiting or mydriasis. The dose and method of giving the drugs, as well as the contra-indications for their use, do not differ from those in the third class of case, under which heading they will therefore be described in detail. It will be enough here if attention is called to two points: (*a*) When scopolamine-morphine has been given, anæsthesia with chloroform is apt to become dangerously deep, and in consequence, Dudley Buxton advises that Harcourt's inhaler should invariably be employed in such cases. (*b*) The first injection should be given two hours before the operation, and repeated in one hour.

3. The procedure usually recommended in parturition may now be described. Different operators vary the detail in slight degree, but on the whole there is considerable agreement as to the most satisfactory method. When the pains become regular, ·0003 gm. scopolamine-hydrobromide and ·01 gm. morphine-hydrochloride are injected. The patient is placed in a darkened, quiet room, and some, in order to insure freedom from sudden interrupting sounds or sights, plug the ears with cotton-wool, and place dark glasses over the woman's eyes. Others merely place a towel over the face. In about ten to fifteen minutes the patient should become somnolent, and in one hour to one hour and a half it is usual to repeat the dose of scopolamine, but the morphine is usually not given after the initial injection. The effect of these doses usually

lasts some five hours, but if it is observed to be passing off, a further injection of scopolamine alone may be given. Four or five doses may in this manner be given at three or four hours' interval,* but as a rule so many are quite unnecessary. Lehmann,† in 70 cases, found that 45 women required two injections, 13 three, and 12 only one. The period of labour varied from one to forty-three hours. The indications for a second injection are increase in perception of pain, and ability to remember an object a short time after it is brought into notice. As a rule, before any operative interference, the patient should be shown some small object, and be questioned some fifteen to thirty minutes later to see if she remembers it. Failure of memory is an indication of complete reaction to the drug, the reverse shows that a further dose is necessary. The solutions used are generally made of such a strength that ½ to 1 cc. is the volume to be injected at a time. The total of scopolamine-hydrobromide should not be more than ·001 gm.

Before pronouncing judgment upon a method which has been much praised in certain Continental clinics, and which is undoubtedly interesting and original from the pharmacological point of view, it will be necessary to consider in detail various points which can be gathered from a study of the published papers.

(*a*). In the first place, as regards the mother, it

* Klein, *Aerztl. Vierteljahres Rundschau*, July, 1906.

† *Zeitschr. f. Geburtsh. u. Gynaekol.*, lviii., 2, p. 297, 1906.

may be said at once that scopolamine-morphine has been known to produce fatal results, though the figures given do not relate solely to puerperal cases. Roith* collected 4000 cases from the literature, with 18 deaths, of which, in the author's opinion, only four were not attributable to the anæsthetic. Making this allowance, the mortality works out at ·35 per cent, or 1 in 285·7. Untoward symptoms are sometimes observed, which though not fatal, may be serious. The commonest are cyanosis and cardiac disturbance (rapid and irregular pulse), which was observed by Preller†—an advocate of the method—in 20 to 25 per cent of the cases, and may go on to delirium cordis if the drug is not discontinued. Vomiting, motor unrest going on to delirium with hallucinations, and general heightening of reflex excitability occur in some cases. Minor disturbances of function consist of extreme thirst, dryness of the tongue, and suppression of sweat and saliva, prolonged narcosis, and post-analgesic weakness. The symptoms in this somewhat formidable list are variously attributed to overdosage, impurities in the drug, and individual susceptibility.

The frequency of cyanosis, in cases where untoward symptoms occur, has its counterpart experimentally in certain observations of Jamieson's on cats.‡ He found that the normal therapeutic dose (given intravenously) produced marked slowing of the respiration-

* q. O. Seifert, *op. cit.*, iii., p. 19.
† *Münch. med. Woch.*, liv., p. 161, 1907 (i.).
‡ *Brit. Med. Jour.*, 1910, i., p. 742.

rate after ten minutes, while a second injection given half an hour after the first, and containing only half quantities of the active drugs, still further reduced the rate in about three minutes. The blood-pressure was not affected. Large doses (thrice the normal amount) caused immediate respiratory standstill and fall of blood-pressure; the animal could only be kept alive by artificial respiration, the spontaneous breathing returning after an hour.

As regards the proportion of cases in which scopolamine-morphine succeeds in producing the desired result, the following table, which is based upon the observations of those who advocate this method, may be consulted :—

AUTHOR	NO. OF CASES	COMPLETE SUCCESS	PARTIAL SUCCESS	FAILURE
Lehmann, *Zeitschr. f. G. u. G.*, lviii., 2, p. 297, 1906	70	61·6 %	37 %	1·4 %
Gauss, *Münch. med. Woch.*, liv. 4, 1907, p. 157	1,000	71·2 %	—	—
Preller, *Münch. med. Woch.*, liv., 4, 1907, p. 161	120	70 %	18 %	12 %
Bass, *Münch. med. Woch.*, liv., 4, 1907, p. 519	107	64·5 %	21·5 %	14 %
Beruti, *Mediz. Klin.*, April, 1909	600	65 %	21·83 %	13·16 %

The authors quoted explain that many of the "failures" are due to the patient being too far advanced in labour for the drug to get time to act. In many individuals two or more injections must be given, and consequently several hours elapse, before analgesia is obtained. It will readily be seen therefore, that in deciding between the relative advantages of chloroform and scopolamine-morphine, these cases tell against the latter, and must rightly be classed as "failures."

According to most observers, the contraindications are primary or secondary uterine inertia, respiratory or cardiac disease, severe cachexia, anæmic conditions, fever, kidney diseases, eclampsia, and any state of marked somnolence.

(*b*). As regards duration of labour, scopolamine-morphine appears to have but little effect; it is said, however, to prolong the first stage of labour very slightly, and to tend to put the abdominal muscles out of action.

(*c*). As regards the child, it appears from the published results that there is a considerable danger of more or less marked respiratory depression, which may end fatally. Holzbach's* experiments showed that as little as ·000000481 gm. scopolamine would cause mydriasis in a new-born infant, but that 30 gm. (rather more than one ounce) of colostrum from a woman who had had an ordinary dose of scopolamine during delivery, would contain at least ·0000025 gm.

---

* *Münch. med. Woch.*, liv., 25, 1907, p. 1228.

Traces could be found in the urine of the infants for the first three acts of micturition. He concludes that cyanosis is a toxic symptom due to the circulation of scopolamine in the infant's blood, which passes off as the drug is excreted by the kidneys.

The following table shows the effect on a number of infants :—

AUTHOR	NO. OF INFANTS	ASPHYXIATED	PARTIALLY ASPHYXIATED (OLIGOPNŒIC)	REMARKS
Lehmann	70	13·3 %	10 %	
Gauss	500	6·3 %	12·7 %	
Preller	120	·8 %	5 % apnœic ; 25 % oligopnœic	25 per cent slight toxic symptoms. 1 death soon after birth—not due to drug.
Bass ..	107	4 %	3 %	A few children drowsy ; 2 died, not due to drug ; 1 died, owing to drug.

Thus it is seen that, by employing scopolamine-morphine, some 60 to 70 per cent of labours may be rendered painless ; that there are numerous contra-indications to the method, and not a few serious disadvantages to the mother, and that about 20 per cent of the children are born with more or less severe

respiratory depression. Under these circumstances it is not to be wondered at that even some of the German advocates of the method recommend its restriction to hospital practice, and that in this country, at any rate, where some attention is given to instructing medical students in the administration of chloroform, this last procedure appears on the whole to offer a greater measure of comfort to the mother, at a far less risk to herself and her offspring.

CHAPTER VII.

ANTIPYRETIC DRUGS:—(I.) The Quinine Group; (II.) The Acetanilide Group; (III.) The Phenacetin Group; (IV.) The Phenyl-Hydrazine Group; (V.) The Antipyrin Group.

ANTIPYRETIC DRUGS.

IN a large number of instances it will be found that the synthetic drugs which influence pyrexia also influence pain, and that many which were originally introduced to reduce the former condition are usually prescribed, in this country at any rate, to alleviate the latter. The number of substances which have been from time to time introduced and exploited as ideal antipyretics is very considerable; but the vast majority of them, even if they possess no definite disadvantages in practice, are utterly devoid of any reasonable claims to special superiority. It should, too, be recognized that the effect produced on the temperature in pyrexia is not always due to the same pharmacodynamic action, and that in selecting an antipyretic drug, the mode by which the fever is reduced must to a great extent determine our choice. The general mode of action of the various groups will be indicated as they are described.

As close on fifty chemical substances will be mentioned in this chapter, some classification will be required in order to present them to the reader's

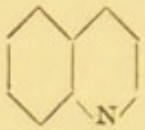
mind in a comprehensible manner. The classification which seems at once most rational and most practically convenient, is that based on their chemical structure; and, although to those who have not been accustomed to deal with the formulæ of organic substances for some years, this may appear a difficult and embarrassing method, the grouping will be rendered clear when it is seen that in almost every large division some well-known drug occurs, which may be taken as a type, and of which all the others are merely modifications, more or less similar in construction. Thus, the first group will be represented by quinine, the second by acetanilide or antifebrin, the third by phenacetin; the fourth alone will contain no typical drug, and the fifth will be represented by phenazone or antipyrin.

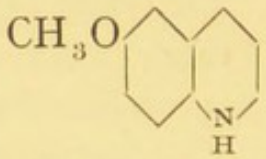
I.—THE QUININE GROUP.

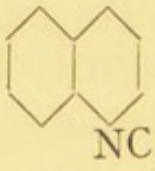
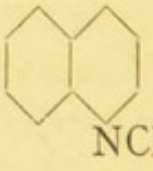
This group of drugs differs from all the others in several important respects. In the first place these substances are not analgesic; and in the second place, their action in reducing a febrile temperature is not analogous to that of the true antipyretics of the other groups, but depends on the fact that quinine and similar bodies are powerful protoplasmic poisons. The specific action of quinine in malaria is, of course, a special application of its toxic effect to the *Plasmodium malariæ;* its action in other forms of fever is due to its inhibitory effect on protoplasmic activity, decreasing cell change and consequently lowering the output of heat. A slight vasodilatation

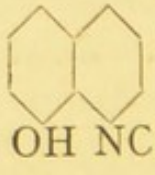
may accompany this, and so aid in the antipyresis by increasing heat loss. The drugs included in this group may be considered in two main divisions :—

1. The Older Quinine Substitutes.

These are derivatives of quinoline  which constitutes one portion of the complex quinine molecule, and is itself an antipyretic of the same type, though too toxic for use in medicine.

Thalline  has no specific action in malaria, and though a powerful antipyretic, is a dangerous drug, causing extensive destruction of the erythrocytes, and damaging the kidney. The dose of the sulphate, a yellowish, crystalline body soluble in seven parts of water, was ·2 to ·3 gm. (3 to 5 grains) ; but its use has been abandoned owing to its obvious disadvantages and the introduction of better drugs.

Kairolin A  and **Kairolin B** 

in the form of sulphates, and **Kairine**  , though not acting on the kidneys, have also been

abandoned owing to their action on the blood. **Analgene** (also called benzanalgene, chinalgene, and labordine) a still more complicated quinoline derivative, is a white, insoluble, crystalline powder, the dose of which is ·05 to ·3 gm. (1 to 5 grains) It is still occasionally used in spite of its toxic action on the red blood-cells and the production of urobilinuria. Nausea, vomiting, diarrhœa, and congestive headache are liable to be set up, unless the drug is used with caution (Seifert).

Thermifugine, the sodium salt of a somewhat similar body, is a soluble, crystalline powder, given in doses of ·1 to ·25 gm. (1½ to 3 grains); it is antipyretic, but also acts on the heart and vessels, raising the blood-pressure and slowing the pulse. It is very seldom used.

2. The Newer Quinine Substitutes.

These may be again subdivided into two groups, according as they are (*a*) insoluble or (*b*) soluble in water. The insoluble bodies have the advantage of being tasteless; the soluble ones were originally intended for hypodermic injection. It is, however, not possible to produce a salt of quinine or any quinine-like body which is both tasteless and soluble, one characteristic being always present in inverse ratio to the other.

(*a*). **Euquinine,** $C_2H_5COO.Q.$,* the propionic acid ester of quinine, is hardly soluble in water, and

* In these formulæ the complex quinine molecule will be represented by the symbol Q.

has only a faintly bitter taste. It contains about 81 per cent of quinine, and is not decomposed till it reaches the intestine, which prevents it from setting up digestive disturbances. It is said also not to cause headache or tinnitus, but possibly this is owing to the usually lower dosage, as Seifert mentions occasional instances in which gastric trouble and singing in the ears have occurred. Besides its general antipyretic effect, it may be employed in malaria as a specific, and according to Laumonier* is much used by the Italian physicians. It has also a stimulating action on the blood-forming organs when given during any length of time. As to dosage, it is stated by v. Noorden to be about half as active as a soluble quinine salt. Adults can take ·25 to 1 gm. (3 to 15 grains) once or twice daily, children ·1 to ·15 gm. ($1\frac{1}{2}$ to 2 grains); the larger doses are only suitable for malarial cases. It may be given in cachets, or the slightly bitter taste be covered by syrup, milk, or cocoa.

Aristoquin $CO\langle^{O.Q}_{O.Q}$ is a white powder, quite insoluble and therefore quite tasteless, containing about 96 per cent quinine. It is broken up in the stomach and not reprecipitated in the intestine, while its excretion is not so rapid as that of the hydrochloride of quinine. It occasionally gives rise to tinnitus, mental confusion, and giddiness, as well as to gastric pain, vomiting, and shivering. The dosage is the same as that of euquinine.

---

* *New Methods of Treatment*, trans. by H. W. Syers, 1904.

Saloquinine is the salicylic acid ester of quinine, and consequently has the formula $C_6H_4\langle^{OH}_{COO.Q}$

It consists of colourless, insoluble crystals. The amount of quinine it contains is of course much smaller than that in the two previous compounds (68·5 per cent). It is said to cause unpleasant bye-effects more frequently. These may be either digestive disturbances (pain and vomiting) due to the quinine, or deafness and tinnitus due to the salicyl. It is soluble in dilute acids, and so decomposed in the stomach. The dose is ·5 to 1 gm. (8 to 15 grains) thrice daily in cachets. A salicylate of saloquinine has also been prepared, which will, of course, contain still less quinine. These compounds do not appear to present any great advantages.

Quinaphthol, composed of a sulphate of β-naphthol and quinine, is a yellow powder, slightly soluble in hot water, and containing about 42 per cent of quinine. It is given in doses of ·5 gm. (8 grains) several times daily as an intestinal antiseptic, in pill form or in cachets. It is not decomposed in the stomach, and first becomes split up into its components in the small intestine. It presents no particular advantages.

Quinaphenin, a compound of quinine and phenetidin, is a white, tasteless, and almost insoluble powder, which may be given in doses of ·15 to ·3 gm. (2½ to 5 grains) in chocolate tablets, milk, or cachets. Its tastelessness is its only advantage. It contains 78 per cent quinine.

(*b*). The synthetic soluble quinine compounds are two in number. The first is called **Quinopyrin,** and is a compound of quinine hydrochloride and antipyrin. It cannot be administered by the mouth, as it is too toxic. Hypodermically the dose is ·5 to 1·5 gm. (8 to 24 grains). The second is a compound of quinine and urea, called quinine-hydrochloro-carbamide. It is soluble in 1 part of water, and the dose is ·6 gm. (10 grains) by the mouth, or hypodermically ·6 to 1 gm. (10 to 15 grains) in sterile distilled water.*

These two compounds have no real advantages over the simple salts of quinine, some of which (e.g., the bisulphide or acid sulphate) are quite sufficiently soluble for subcutaneous use. The first has the great disadvantage of a high degree of toxicity, and the second, owing to the urea present in the molecule, contains very little quinine.

II.—THE ACETANILIDE GROUP.

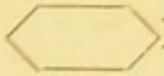
The antipyretics of this and the following groups are so in the true sense of the word; that is, they act directly on the thermotaxic centre, which effects, under their influence, a general dilatation of the cutaneous vessels and consequent increase of heat loss. In pyrexial conditions, the thermotaxic centre is so altered in function that increased heat production is not met by a *corresponding* increase in heat loss, though it retains its general sensitive-

* This body has recently been employed as a local anæsthetic in rectal surgery. A report on 102 cases by Hirschman is reviewed in the *Lancet*, 1910, ii., p. 576.

ness to alterations in these processes. The true antipyretics, then, tend to restore the centre to its usual ratio of reactivity, at any rate temporarily. Thus they act differently from protoplasmic poisons like quinine on the one hand, and measures such as external refrigeration, which affect only the peripheral mechanism, on the other. In this group the drugs are all, like **Acetanilide,** derivatives of **Aniline,** itself a powerful antipyretic, though too toxic for therapeutic purposes. Among the more important physiological effects of aniline is the extensive breaking down of the erythrocytes and the liberation of hæmoglobin in the blood. This property is transmitted in a greater or less degree to its chemical derivatives.

The relationships of these bodies may be seen by the following structural formulæ :—

aniline

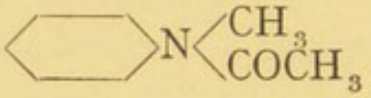


acet-anilide.

Cosaprin, a compound of acetanilide and sodium sulphonate, is a white, crystalline body which has the advantage of solubility in water. The dose is ·05 to ·5 gm. (¾ to 8 grains). It is quite useless as an analgesic, and very feeble and transient as an antipyretic. This is due to its chemical composition, which causes it to be broken up in the body into a sulphur-containing substance called sulphanilic acid, which is inert. It also gives rise to unpleasant perspirations.

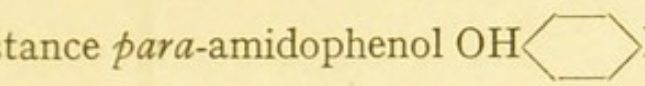
Euphorin is a compound of aniline with urethane; it resembles acetanilide in its physiological action, but does not show the hypnotic properties of urethane. It is a colourless, crystalline powder, slightly soluble in water; the dose is ·05 to ·5 gm. (¾ to 8 grains). It is an efficient antipyretic and analgesic, and being soluble in alcohol may be prescribed in white wine or whisky, which will conceal its slightly burning taste. Larger doses are occasionally given, as much indeed as 1 gm. (15 grains).

Exalgin is an aniline derivative of rather more complex structure than acetanilide, both the hydrogen groups of the amide or NH_2 radicle being replaced.



It consists of colourless crystals, somewhat soluble in water, and more so in alcohol, the usual dose being from ·1 to ·3 gm. (1½ to 5 grains); but as much as ·8 gm. (12 grains) may be given. Though similar to acetanilide in therapeutic action, it is far more toxic. Dizziness, a feeling of intoxication, flashes of light before the eyes, tinnitus, sweating, myosis, and albuminuria are not infrequently set up, while in more severe cases, salivation and epileptiform convulsions occur. It causes death by respiratory failure. It is therefore not a satisfactory drug. In cases of poisoning, 30 grains of sodium salicylate may be given, which forms an inert compound with exalgin, and atropine may be injected hypodermically.

III.—THE PHENACETIN GROUP.

These bodies are all derivatives of the well-known chemical substance *para*-amidophenol  , which differs from aniline only in the possession of a hydroxyl group at the opposite end of the benzene ring (*para* position). In their passage through the organism, aniline, acetanilide, and all their derivatives possessing an antipyretic action, are partially converted into this substance, which has powerful antipyretic properties. The activity of any of these drugs, therefore, will be found to be roughly proportional to the amount of *para*-amidophenol formed in the body, and the rate at which this reaction takes place. At the same time, the toxicity is to a great extent similarly conditioned, and therefore, the more energetic the antipyretic action the more dangerous any given member of this group of drugs will be, and only among the pharmacologically less active, will be found those which are least likely to cause undesirable symptoms. In spite, therefore, of all which may be said to the contrary by the enthusiastic manufacturers of new *para*-amidophenol derivatives, the practitioner may rest assured that a maximum of efficiency can in no case be combined in this series of bodies with a minimum of toxicity.

There is yet another point to be borne in mind in appraising the value of these drugs. From some, a substance called phenetidin, which closely resembles *para*-amidophenol in composition, is formed in the stomach in varying amount, where it combines

with hydrochloric acid to form the hydrochloride of phenetidin—a highly toxic body. Any derivative from which appreciable amounts of this substance are formed is therefore unsafe for use as a drug. In dealing with the phenacetin group, it will perhaps be convenient to consider them in two main divisions : (*A*) Those which are more stable, less dangerous, and also less effective physiologically ; and (*B*) Those which are more easily broken down, and thus more active, both as drugs and as poisons.

The rate at which these drugs are broken up in the body may be gauged to some extent by noting the time of appearance of their decomposition products in the urine. This may easily be done by testing the urine for *para*-amidophenol and phenetidin.

1. Boil the urine with one quarter its bulk of strong HCl, and when cool, add a few cc. of a 3 per cent solution of carbolic acid, and then a few drops of chromic acid solution ; *para*-amidophenol, if present, will give a red colour, changing to blue in presence of ammonia.

2. Add two drops HCl and two drops of a 1 per cent solution of sodium nitrite : (*a*) Add *a*-naphthol in a little caustic soda solution : a beautiful red colour will result, changing to violet if HCl be added : the depth of the colour produced is roughly proportional to the amount of phenetidin present ; or (*b*) Add phenol, which will give a yellow colour in alkaline solution and a rose red with acids (presence of phenetidin).*

* *Clinical Diagnosis*, v. Jaksch and Garrod, 1905, p. 456.

By this means any new compound of the phenacetin type can easily be classified by the practitioner himself, who can, moreover, become proficient in the performance of these tests by taking a few doses of phenacetin himself and examining his own urine from time to time, after a few hours have elapsed.

1. Stable Substances.

Triphenin (proponyl phenetidin) is similar to phenacetin, though, owing to the slowness with which it is absorbed, its action is much feebler. The dose is ·5 to 1 gm. (8 to 15 grains) in a cachet. It is also said to have some effect as an intestinal antiseptic.

Salophen or **Salophenin** (salicyl phenetidin) is a white crystalline substance, possessing neither taste nor odour, and almost insoluble in water. It is first decomposed in the small intestine, and is mostly excreted unchanged in the urine. Its insolubility renders it a very inert drug, and its main action is due to the 51 per cent of salicylic acid which it contains. The dose is ·6 to 2 gm. (10 to 30 grains). It has also been employed as a 10 per cent ointment in psoriasis. Toxic symptoms are rare, and include profuse sweating, mental confusion, faintness, tinnitus, nausea, and slow pulse (Seifert). Huot* reports 35 cases of acute rheumatism in which he employed this drug with good results in place of

* Abstr. *Schmidt's Jahrbuch*, 248, p. 125, 1895.

sodium salicylate. The average dose was 3 to 4 gm. (45 grains to 60 grains) in twenty-four hours. Drews* gave it in even larger doses (up to 90 grains or 6 gm.) to patients suffering from the nervous type of influenza. Koster† gave similar doses in rheumatic cases. Others have used it with success in headache, neuralgia, and migraine, but full doses seem necessary in all cases.

Amygdophenin, a similar compound, in which mandelic acid takes the place of salicylic acid, is a light, whitish-grey powder, only slightly soluble in water, and very feeble as an antipyretic. The dose is ·5 to 1 gm. (8 to 15 grains). In acute rheumatism Stüve‡ gave 3 to 6 gm. (45 to 90 grains) per diem, and noted that it occasionally caused dizziness. It may also occasionally produce faintness, tinnitus, and severe sweating.

Apolysin is a citric-acid compound, and occurs as a yellowish-white, granular powder, not very soluble in cold water. Hildebrandt§ states that whereas it is much less easily broken up than phenacetin when in alkaline media, the reverse is the case in the presence of dilute acids. For this reason 1 gm. (15 grains) given subcutaneously to a small dog gave rise to no *para*-amidophenol or phenetidin in the urine. Moreover, though feeble and uncertain in its action as an antipyretic and analgesic, it forms

---

* *Centralbl. f. innere Med.*, xvi., 47, 1895.
† *Ther. Monatsh.*, viii., 1, 1894.
‡ *Centralbl. f. innere Med.*, xvi., 46, 1895.
§ *Ibid.*, xvi., 45, 1895.

phenetidin hydrochloride in the stomach, which may set up toxic symptoms. The dose is ·5 to 2 gm. (8 to 30 grains).

Kephaldol is said to be a compound of citric and salicylic acids with phenetidin, and to contain also some quinine. It is a yellowish-white, bitter powder, but slightly soluble in water, and is sold in ·5-gm. (8-grain) tablets, one to four of which may be given as a dose, with a total of six per diem as a maximum. After its use, severe sweating, nausea, and vomiting have occasionally been observed,* so possibly the toxic hydrochloride of phenetidin is formed in the stomach.

Phenosal is a compound of salicylacetic acid (aspirin) with phenetidin; it contains 57 per cent phenetidin and 43 per cent salicylic acid; it is a white, crystalline, bitter powder, very insoluble in water, and possessing only slight physiological action. The dose is ·5 gm. (8 grains). The only unpleasant effect observed is excessive sweating. Burghart,† who has reported on twenty-seven cases, gave ·5 to 2 gm. (8 to 30 grains) a day without ill effects.

Salocoll is another compound containing salicylic acid. It is a derivative of phenocoll (*q.v.*), and is very insoluble and thus inert. It is a sweetish, white, crystalline powder, the dose of which is ·8 to 2 gm. (10 to 30 grains).

Malakin, a compound of salicylaldehyde and phenetidin, is almost insoluble in water; it occurs as

* O. Seifert, *op. cit.*

† *Deut. med. Woch.*, xxiv., 41, 1898.

light yellow, crystalline needles, practically insoluble in water, so that it is best administered in cachets. The dose is ·8 to 2 gm. (10 to 30 grains) thrice daily. Its action is slow, and the analgesic effect more marked than the antipyretic. Probably the salicyl nucleus is the more effective portion of the molecule. It may produce severe sweating, and indigestion. It is decomposed by dilute acids, and is somewhat rapidly excreted, the urine showing traces of salicylic acid in twenty minutes.*

Eupyrin, a compound of phenetidin and vanillin-ethyl carbonate, has but slight physiological action. It is not toxic, and causes little formation of met-hæmoglobin, if indeed it acts as a blood poison at all. The vanillin is said to give it a refreshing effect; it is useful as a mild antipyretic, especially for children, but is of no value as an antineuralgic. The dose is about 1 gm. (15 grains), and should in no case exceed 2 gm. (30 grains).†

Neurodin is a urethane derivative; it is a white, crystalline substance, hardly soluble in water and correspondingly inert physiologically. The dose is ·3 to 1 gm. (5 to 15 grains). It has been employed mainly as an analgesic; when used as an antipyretic, cyanosis and severe sweating are apt to occur.

Thermodin is a similar body, only differing from neurodin in containing one more ethyl group. It is very insoluble except in acids, and should be combined with acetic acid and syrup. It is said to be

* *Pharm. Jour.*, vol. xxiv., p. 507.

† Overlach, *Centralbl. f. innere Med.*, xxi., 45, 1900.

a mild antipyretic, with no depressant action on the medullary centres. The dose is ·3 to 1 gm. (5 to 15 grains). Its analgesic action is very weak, and it is a feeble diuretic. It may be dissolved in acid media, and is best given with 10 to 15 minims of acetyl chloride, syrup, and water up to 5 oz., this making a pleasant drink, similar to lemonade.*

2. Unstable Bodies.

Lactophenin (lactyl phenetidin) has a similar action to antipyrin, but is more soluble. It was at one time much used by v. Jaksch in cases of enteric.† He states that as much as 6 grams (90 grains) may be given daily without harm. The narcotic action is more marked than the antipyretic. It occurs as white, tasteless crystals, with a slightly bitter taste, and is given in doses of ·3 to 1 gm. (5 to 15 grains); in rheumatism, Róth‡ recommends doses up to 5 gm. (75 grains) per diem; and in mental cases larger doses, up to 9 gm. (135 grains) daily have been given.§ In children it has been given in fairly full doses (·3 to ·5 gram or even 1 to 2 grams thrice daily) for pneumonia (Heim), but it is liable to cause the formation of hydrochloride of phenetidin in the stomach, and doses of 5 gm. (75 grains) per diem have set up toxic symptoms (dizziness, with rapid and intermittent

* Spineanu, *Brit. Med. Jour.*, epit. 64, 1906, i.
† *Centralbl. f. innere Med.*, xv., 11, 1894.
‡ *Wien. klin. Woch.*, vii., 37, 1894.
§ Foerster, *Psychiatr. Woch.*, i., 38, 1899.

pulse and flushing) lasting about three-quarters of an hour.* Cyanosis, vomiting, collapse, and sweating are sometimes observed (O. Seifert).

A curious and unpleasant bye-effect which appears to be not very uncommon after the administration of lactophenin is jaundice. Strauss† observed three cases, in all of which large doses had been given, namely 4 gm. (60 grains) daily, for nine, fourteen, and twenty-one days, and found experimentally that it set up gastroduodenal catarrh in rabbits. Wenzel,‡ who records a case in which only ·9 gm. (13 grains) had been given for a fortnight, attributes the jaundice to the toxic action of the drug on the blood. Laache§ notes that, though jaundice usually occurs after large doses, this is not invariably the case, and in one instance it appeared after only 5 gm. (75 grains) had been taken. He believes that it is variously caused, sometimes by digestive disturbances and blocking of the large bile-ducts, and sometimes by a destructive action of the drug on the liver-cells, and occlusion of the smaller passages. The jaundice is always accompanied by a sharp rise of temperature, which falls again very rapidly. The cases invariably recover. Hahn,‖ who observed two cases, collected sixteen from the literature. His conclusions do not differ as to prognosis from Laache's.

---

* Wefers, *Deut. med. Woch.*, xxiii., 29, 1897.
† *Ther. Monatsh.*, ix., 9, 1895.
‡ *Centralbl. f. innere Med.*, xvii., 6, 1896.
§ *Deut. med. Woch.*, xx., 49, 1894.
‖ *Ibid.*, iv., 9, 1898.

Citrophen or **Citrophenin** is a fine, white, crystalline powder, soluble in forty parts of water, and possessing an agreeable taste. Its chemical nature seems somewhat uncertain, as is its toxicity. A case is quoted by Laumonier* in which 1 gm. (15 grains) produced marked toxic symptoms in a young woman, with severe headache, sweating, and cyanosis, due to the formation of methæmoglobin (Schrotten). A number of other cases have been collected by O. Seifert in which similar symptoms were noted, as well as tinnitus, cardiac weakness, arrhythmia, cold extremities, and exhaustion. The cyanosis which seems a marked feature in these cases, may last for three days. In Heyde's† case, that of a well-built, healthy young man of 22, 1 gm. (15 grains) was taken in powder overnight, and a second similar dose after breakfast the next morning. The symptoms, which were severe and typical, set in one hour later. These were, cardiac weakness and arrhythmia, extreme cyanosis, cold extremities, and sweating. He recovered in four or five days. His father was known to have an idiosyncrasy against phenacetin. In Goldschmidt's‡ case the patient was a woman who bought five 1-gram citrophen powders at a chemist's, and took four of them one after the other to relieve a toothache. Shortly afterwards she collapsed, with severe rigors, sweating, subnormal temperature, weak irregular pulse, and

* *Op. cit.*, p. 292.
† *Münch. med. Woch.*, liv., 33, p. 1640, 1907.
‡ *Ibid.*, 23, p. 1129.

cyanosis of the face and hands. Under vigorous stimulation she recovered, but the cyanosis persisted for twenty-four hours. There were no symptoms of intestinal or renal irritation, though others have noted these occurrences.

In spite of these obvious defects, citrophen has been somewhat largely employed, and Laumonier* speaks highly of its antipyretic action in ordinary acute fevers; though in tuberculosis he considers the profuse sweating which accompanies the fall of temperature to be too exhausting to the patient. As an analgesic, he thinks it acts well in acute rheumatism, and quotes other authors who have found it valuable in the headache of chlorosis and in various forms of neuralgia. It has also been given rather largely to children for whooping-cough, but according to Tittel† and Feuchtwanger‡ it does not cut short the attack, even if given in the early stages, and the effect passes off at once when the drug is discontinued. Telegdi§ found it useless in epilepsy and delirium, though of use as an antipyretic.

Citrophen may be prescribed in cachets or as a 2 per cent solution; the dose is ·5 gm. (8 grains) two, four, or even six times in twenty-four hours. The dosage for children is given as: Infants, ·1 gm. (1½ grain); from 1 to 3 years of age, ·15 to ·3 gm.

---

* *Op. cit.*

† *Wein. med. Presse*, xli., 29, 1900.

‡ *Der Kinderarzt*, xi., 8, 1900.

§ Schmidt, *Jahrbuch*, 271, p. 179, 1901.

(2 to 4 grains) ; for older children, ·4 to ·5 gm. (6 to 8 grains) three times a day. Schreiner* suggests ·15 to 2 gm. (2 to 3 grains) for every year of life to begin with, the dose being rapidly raised to ·3 gm. (4 grains). Homberger† states that rather larger doses are required to produce an analgesic effect (up to 30 grains or 2 gm. per diem) than those required to lower the temperature. Hildebrandt‡ regards citrophen as a simple citrate, just as toxic as any other phenetidin salts, the base in this form being in fact more toxic than twice the amount in the form of phenacetin. This judgment appears to be justified by the cases already described.

Phenocoll is glycocoll phenetidin (or amidophenacetin), the hydrochloride of which is a white, crystalline powder, forming watery solutions with a bitter taste. Being soluble, it acts rapidly, and is said to be a more powerful analgesic than phenacetin. On the other hand, elimination being also rapid, its effects are transitory. (The urine fails to give any reaction with ferric chloride after twelve hours).§ It has been employed in various febrile and painful affections, and also given to children in cases of pertussis. The ordinary dose is ·5 to 1 gm. (8 to 15 grains) for adults. Children may be given ·03 to ·12 gm. (½ to 2 grains) every two hours.

It is, however, a somewhat toxic body. O. Seifert

---

* *Ther. Monatsh.*, xvii., 5–7, 1903.
† *Deut. med. Ztg.*, No. 76, 1896.
‡ *Centralbl. f. innere Med.*, xvi., 45, 1895.
§ *Pharm. Jour.*, vol. xxi., p. 977, 1891.

quotes authors who have frequently observed nausea and vomiting and an erythematous rash, and mentions Lewin's opinion that, owing to the danger of collapse, it should be given to children only with the greatest caution.

Cryofin is methyl-glycol-phenetidin, and consists of white, tasteless, and inodorous crystals, easily soluble in water. The dose is ·5 to 1 gm. (8 to 15 grains). It is said to be effective in half the doses usually necessary with phenacetin, but its action is transitory. It has occasionally given rise to collapse and cyanosis (O. Seifert).

Malarin is a citric acid salt of methylbenzylidene phenetidin. It is a yellowish, crystalline, bitter-tasting body, soluble in water, and is given in doses of ·4 gm. (6 grains). Its action is rapid, and it has marked toxic effects. The original substance is almost insoluble and only slightly toxic.*

Pyrantin, a succinic acid derivative of phenetidin, is used in the form of soluble sodium salts, and intended for subcutaneous injection. It occurs as a glistening, crystalline powder with a sweetish taste, the dose of which is 1 to 3 gm. (15 to 45 grains). Gioffredi† states that large doses in experimental animals cause a paralysis, starting in the brain and passing downwards to the cord. Small doses have no effect on the heart and respiration, but large ones retard both. With very large doses, there is a fall of blood-pressure owing to peripheral vasodilatation.

---

* Schwartz, *Prag. med. Woch.*, xxiii., 37–8, 1898.

† *Deut. Arch. f. klin. Med.*, lx., 6, p. 559, 1898.

The antipyretic action is due, partly to increased heat loss and partly to decreased heat production, which is attributable more to its action as a protoplasmic poison, retarding all metabolism, than to any direct effect on the thermotaxic centre. Daily large doses have no action on the blood. It is excreted as phenetidin and succinic acid. Its antipyretic action is usually regarded as uncertain.

Phesin is the result of an attempt to increase the solubility of phenacetin by the introduction of a sulphonic acid group, which is a very usual method of producing this effect in organic bodies. It is a sodium salt of phenacetin sulphonic acid, and occurs as a light brown, soluble powder, with a somewhat salt, stinging taste, the dose of which is 1 to 2 gm. (15 to 30 grains), or up to 6 gm. (90 grains) in twenty-four hours. It is, however, but a feeble antipyretic and analgesic ;* it is liable to produce much sweating, and in spite of its solubility, it cannot be used hypodermically owing to the pain and infiltration it sets up at the site of injection (O. Seifert).

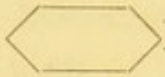
IV.—THE PHENYLHYDRAZINE GROUP.

Phenylhydrazine, though not used in medicine, is well known in the physiological laboratory owing to the crystalline compounds it forms with various sugars, whereby they may be microscopically identified and distinguished.

---

* Lentz and Tendlau, *Berl. klin. Woch.*, xxxv, 40, 1898.

Its structure is represented thus :—



and its marked chemical reactivity makes it an extremely toxic body. It is a powerful protoplasmic poison and, like aniline, causes hæmolysis, with the formation of methæmoglobin and other bodies. A substance known as allantoin appears in the urine, and in fatal cases death takes place from cerebral paralysis and convulsions. But few modifications of phenylhydrazine have been introduced into medicine, and none of these have shown themselves satistactory drugs in practice. All are blood-poisons, and it does not appear likely that any further derivatives will be introduced of more practical pharmacological value.

Antithermin, a lævulinic acid compound, consists of colourless crystals possessing a somewhat burning taste. It is far too toxic for practical purposes, and is also apt to irritate the gastric mucosa.

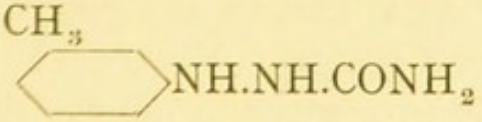
Orthin is another modification in which carboxyl and hydroxyl groups are introduced into the ring. It is uncertain in action and liable to produce toxic symptoms. The original substance is very unstable, but the hydrochloride, which occurs as colourless, soluble crystals, is more easily kept from decomposition.

Agathin is somewhat less toxic than the other phenylhydrazine derivatives, and contains a salicyl nucleus. It is a yellowish-white, crystalline powder, insoluble in water, and possessing neither taste nor

odour. Among the toxic symptoms it may produce are nausea, headache, sweating, flushing of the face, sleeplessness, and a burning sensation during micturition (Seifert). The ordinary dose is ·2 to ·5 gm. (3 to 8 grains); but usually, large doses are required to produce an analgesic action, as it is a substance which is only with difficulty broken down in the body.

Pyrodin, the acetyl compound of phenylhydrazine, is a more powerful analgesic than antipyrin, antifebrin, or phenacetin, and has considerable antipyretic power, but it is liable to produce jaundice and hæmoglobinæmia, and is generally too toxic for practical use. The maximum dose is ·15 gm. (2 grains).

Maretin differs from the other phenylhydrazine compounds in possessing a methyl group introduced into the benzene ring in the *meta* (or 1 : 3) position. The amido group is also combined with carbamic acid (NH_2COOH). Its structure, therefore, is



(*meta* toluyl hydrazine carbamate). It occurs in white, shining crystals, very sparingly soluble, and without taste. The dose is ·2 to ·5 gm. (3 to 8 grains).

The behaviour of maretin in the animal organism has been investigated by Dreser,* in order to ascertain

* *Mediz. Klinik.*, 1908, No. 44, p. 1684.

what would be a safe dosage. He found that, up to half a gram per diem, maretin was entirely eliminated in the urine within twenty-four hours. This, therefore, should be considered the maximum safe dose; larger doses lead to accumulation of the drug in the body. Occasionally, a yellow oxidation product is found in the urine, and a yellowish tinge is noted in the skin. In other cases, severe and genuine jaundice is set up, with collapse. Brinda,* who made a number of experiments on animals in order to test the action of this drug, showed that it produced a slight fall of blood-pressure, apparently due to a weakened cardiac action. He did not obtain any evidence of a toxic action on the blood. It produces in the urine a reducing substance which can be tested by Fehling's solution. A number of German authors† have reported favourably on its clinical use in tuberculosis and acute rheumatism. In the former it is said to produce much sweating, but not in the latter.‡ It is said to be useless in gonorrhœal rheumatism.§ It is also an analgesic in doses of ·25 to ·5 gm. (4 to 8 grains). Valenti,‖ as the result of careful experiment, gives a single daily dose to children of ten to twelve years of ·25 gm. (4 grains), or the same amount in half doses with two or three hours' interval between them. Smaller doses have

---

* *Giorn. della R. Accad. di Med. di Torino*, Sept. and Oct., 1905.
† Schmidt, *Jahrbuch*, vol. 295, p. 195, 1907.
‡ Kirkovič, *Wien. klin. Woch.*, xviii., 37, 1905.
§ Sobernheim, *Deut. med. Woch.*, xxxi., 15, 1905.
‖ *Gazz. degli Osped.*, Apr. 28, 1909.

some slight effect, but not enough to be of practical service. To adults he gives ·5 gm. (8 grains) in divided doses, with one or two hours' interval, per diem. The blood-pressure is somewhat lowered. After a time the antipyretic action wears off. He does not think that it has any marked advantages over the older antipyretics.

Port* reports a case in which half a gram of maretin was given twice a day and produced marked anæmia after several days. Later a yellowish tinge appeared in the skin, with vomiting, then cyanosis and dyspnœa. The red blood-cells fell to a little over a million per cc.; urobilin and urobilogen were found in the urine. He quotes cases by other observers. The toxic symptoms appeared after :—

·5	gm.	twice	daily	for 9	days
·25	gm.	,,	,,	,, 16	,,
·25	gm.	thrice	,,	,, 7	,,
,,		,,	,,	,, 57	,,

Zille† observed jaundice in two cases after some months, the daily doses being from ·25 to ·5 gm. Kirkovič noted slight and transient jaundice in three patients. Maretin has been mainly given in the earlier stages of phthisis, in which Continental clinicians are in the habit of employing antipyretic drugs to a somewhat large extent. It is probably useless in the more advanced stages.

Diarrhœa and colic, headache, hæmoglobinuria,

* *Deut. med. Woch.*, xxxiii., 1907, 35.
† *Gazz. degli Osped.*, xxvii., No. 144, 1908.

and collapse, are noted as occasionally occurring.*

Cryogenin (*m.* $C_6H_4.CONH_2.NH.NH.CONH_2$) is a hydrazine derivative belonging to the series known as semicarbazides. It is a colourless, crystalline body, with a pleasant taste, like bitter almonds, insoluble in water, and so usually given in cachets. The dose is ·2 to 1 gm. (3 to 15 grains). Its insolubility is probably responsible for the absence of toxic symptoms, and also for the mildness of its antipyretic action.

According to Segre† it is not analgesic in man. One gram (15 grains) produces no effect on the temperature in health, nor indeed on any other function, except a slight increase in the excretion of uric acid and urea. It is very slowly eliminated, and traces can be found in the urine six or seven days after its administration has been stopped; this can be easily determined, as a reducing substance appears in the urine which can be tested with Fehling's solution. If large doses are given for some time, the number of red blood-corpuscles and their hæmoglobin content, are diminished. Segre thinks ·5 gm. (8 grains) three times a day a useful dose.

Gordon,‡ who has employed it in cases of phthisis, admits that it is not a powerful antipyretic, but considers its effect lasting. He states also that after a time it loses its antipyretic power. He usually

---

* O. Seifert, *op. cit.*

† *Gazz. Med. Ital.*, Dec., 1904.

‡ *Lancet*, 1909, ii., p. 1812.

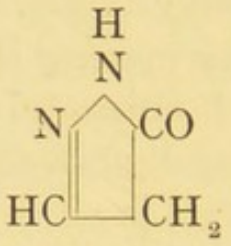
begins with small doses—·3 gm. (5 grains) for adults at 12 noon and again at 4 p.m., gradually increasing the amount, but never exceeding ·5 gm. (8 grains). He says that by this means, the evening rise of temperature can be controlled. Continental physicians usually begin with large doses, and gradually diminish the amount. Thus Boulterville,* in cases of enteric, gave 1 gm. (15 grains) on the first day, ·6 gm. (10 grains) on the second day, ·4 gm. (6 grains) on the third day, and then ·2 gm. (3 grains) daily. This kept the temperature a little above 100° F. Quinine and cold baths were also given. The reports of cases treated by this substance do not differ materially from those published concerning the many other antipyretics which are from time to time put on the market and employed by physicians for a few years. O. Seifert quotes cases in which its administration has given rise to severe sweating, restlessness, depression, and collapse. Hæmoptysis is a contraindication. Large doses slow the pulse, and in a few cases have caused exanthemata.

V.—THE ANTIPYRIN GROUP.

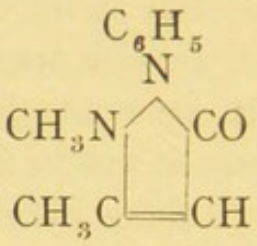
Antipyrin is a derivative of a different class from the other well-known antipyretics, phenacetin and antifebrin. It is derived from a body called pyrazolon, by the substitution of two hydrogen atoms with phenyl (C_6H_5) and methyl (CH_3) respectively; a second methyl group is combined with the

* *Jour. de Méd. et de Chirurg. Prat.*, Nov., 1904.

nitrogen, the double bond between it and the next carbon atom being thus eliminated.

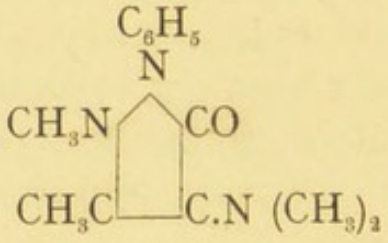


Pyrazolon



Antipyrin

Several modifications of antipyrin have been introduced, mainly in order to obtain a still more powerful drug; but only one appears to present any great advantages. This body is dimethyl-amido-antipyrin, or antipyrin in which the only remaining hydrogen atom in the ring is replaced by the group $N(CH_3)_2$—



Pyramidon

Pyramidon consists of small white crystals, soluble in water, the solutions having a slightly bitter taste. The dose is ·2 to ·5 gm. (3 to 8 grains); ·3 gm. (5 grains) is usually quite effective. It has practically no effect on the heart and circulation, and is thus superior to antipyrin, which occasionally produces cardiac weakness or failure. It increases nitrogenous metabolism, and hence it is suggested that it is better not given to diabetic

patients. Toxic doses have no effect on the red blood-cells, nor is fatty degeneration observed post mortem in animals that have taken large quantities.

German physicians have given pyramidon largely as an antipyretic, especially in typhoid fever and in acute tuberculosis. Thus, in the former disease, Hödlmoser* gives ·2 gm. (3 grains) every three hours to adults, gradually reducing the dose towards the end of the illness. The general effects on the nervous system and the lowering of the temperature are, he thinks, more marked than under a system of hydrotherapy. There is, however, no reason to believe that pyramidon or any other drug can cut short an attack. Some writers find that the excessive sweating produced during the fall of temperature, especially in the tuberculous cases, is weakening and distressing to the patient; to meet this, a compound of pyramidon and camphoric acid has been introduced; but there seems to be little evidence as to its practical utility. In this country, at any rate, antipyretic drugs are not very generally employed as a routine treatment in the self-limited fevers like typhoid, or in the course of a chronic tuberculous infection. It is therefore mainly as an analgesic that pyramidon is used in Great Britain; and generally it may be said that it is often efficacious in all forms of functional disturbance, such as headache, neuralgia, or the pains associated with pelvic disturbances in women. In all cases its action is

* *Wien. klin. Woch.* xviii., 5, 1905.

more powerful than that of antipyrin, in fact it is said to be three times more powerful; but some writers consider it slower in taking effect, though more enduring when its action has been established. Laumonier* says that it takes two hours to produce its result, but this is certainly an over-estimate in cases where the pain is not extremely severe. In ordinary cases it usually acts in about half an hour.

Unpleasant bye-effects are rare, but O. Seifert† has collected the following from the literature: Exanthemata resembling those of antipyrin, cyanosis, vomiting, dizziness, and collapse. In one case death occurred. Pyramidon occasionally gives rise to the excretion of a substance in the urine which, on standing, becomes oxidized to a red pigment, called rubazonic acid.

In cases where pyramidon is not well tolerated by the stomach, it may be administered in the form of an enema, and Bertheraud‡ has given ·01 gm. ($\frac{1}{7}$ grain) hypodermically once or twice a day for the relief of pain in a case of sciatica.

Pyramidon may form coloured solutions with oxidizing agents, and with acacia; it is incompatible with the same bodies as antipyrin. An acid camphorate (·75 to 1 gm., or 12 to 15 grains) and a neutral camphorate (·5 to ·7 gm., or 8 to 12 grains) have also been prepared. They are white,

* *Op. cit.*, p. 286.
† *Op. cit.*
‡ q. Laumonier, p. 289.

soluble salts, the latter of which is the more markedly antihydrotic. They are intended for use in cases of phthisis, where there is pyrexia and much sweating. A salicylate of pyramidon (·5 to ·75 gm., or 8 to 12 grains) intended for use in acute rheumatism, is a white, soluble powder, incompatible with ferric salts. These bodies present no special advantages over an ordinary prescription containing the drugs of which they are composed.

Tussol, the mandelic acid salt of antipyrin, is a white powder, easily soluble in water, the dose of which is ·05 to ·5 gm. (1 to 8 grains). Children under one year can take ·01 to ·03 gm. ($\frac{1}{5}$ to $\frac{3}{5}$ gr.). It was at one time much recommended in Germany as a remedy for whooping-cough, but in reality it presents no advantage over antipyrin, to which Sonnenburger attributes its effect in this disease. It is incompatible with milk and with alkaline mixtures.

Tolypyrin differs from antipyrin in containing one more methyl group; physically it consists of colourless crystals, almost insoluble in water. In dosage and method of administration, it resembles antipyrin. It is, however, a weaker analgesic, and is apt to produce vomiting, owing to its irritant effect on the mucous membrane. *Tolysal* is the salicylic acid salt of tolypyrin, and consists of small, almost colourless crystals, which possess a bitter taste and are but slightly soluble in water. The dose is ·5 to 1 gm. (8 to 15 grains) in cachet or tablet, the maximum for twenty-four hours being 8 gm. (120

grains). **Salipyrin** is a similar antipyrin compound, almost insoluble in water. The dose is ·5 to 2 gm. (8 to 30 grains). These substances have no advantages over a mixture of antipyrin and salicylate of soda. Salipyrin seems not infrequently to give rise to unpleasant bye-effects such as headache, burning pain in the stomach, and nausea; also symptoms of salicyl poisoning, such as deafness and tinnitus; circulatory disturbances, such as slow, irregular pulse, palpitation, and cyanosis; and various eruptions, sometimes of an irrritable eczematous type.*

* O. Seifert, *op. cit.*

CHAPTER VIII.

CERTAIN SPECIFIC REMEDIES:—(I.) Remedies for Phthisis; (II.) Remedies for Acute Rheumatism; (III.) Remedies for Whooping-cough; (IV.) Remedies for Gonorrhœa; (V.) Remedies for Functional Nervous Disorders.

CERTAIN SPECIFIC REMEDIES.

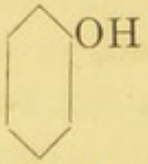
I.—REMEDIES FOR PHTHISIS.

IT is an extremely difficult matter to estimate clinically the effect of any drug on the course of a disease like phthisis. It is seldom that it can be the only means of treatment adopted, as the serious nature of the condition necessitates the use of all measures, such as open-air life, good feeding, etc., which are known to influence it in a favourable manner. Exact observations on any particular symptom, such as the pyrexia, the loss of weight, or the cough, are also difficult to carry out in ordinary practice, while under sanatorium conditions, other factors come into play. The only reliable method by which the value of any given drug can be determined is by the extensive and careful observation of a specially skilled and experienced physician, who can make due allowances for other factors, and has also a very large number of cases on which to make his trials. The evidence thus gained will not be mathematically exact, but will depend for its

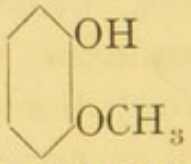
value largely on the personal characteristics of the observer. On the whole, it must be admitted that most of the drugs and methods of drug treatment are more interesting as examples of ingenuity and inventiveness on the part of their introducers, than as remarkably valuable additions to the known means of combating the disease in question. The various groups of substances will be described and their general properties indicated, but no comparative review of their merits is, under the circumstances, possible.

1. Guaiacol and its Derivatives.

Guaiacol itself has long had a reputation as an antiseptic, and has been given internally with a view to checking bacterial and fermentative processes both in the intestinal canal and the bronchi. It is chemically a phenol, only differing from ordinary phenol or carbolic acid by the presence of a methoxy (OCH_3) group. It is less toxic and more powerfully antiseptic than phenol. The structure of the two bodies is shown in the following formulæ :—



Phenol $C_6H_5.OH$



Guaiacol $C_6H_4.OH.OCH_3$ 1 : 2.

The ordinary guaiacol of medicinal practice is a colourless liquid, containing several homologues of guaiacol. Its disadvantages are, that it irritates the gastric mucosa, has a disagreeable taste, and is

insoluble in water. To obviate these undesirable qualities, many modifications of the original substance have been introduced; but though many of them are improvements, they none of them succeed in overcoming all three. Those which are tasteless, for instance, are for the most part insoluble.

The insoluble compounds are :—

Guaiacol Carbonate (Duotal), a white, crystalline powder, insoluble in water, with a slight odour, and no taste. Dose ·2 to ·5 gm. (3 to 8 grains).

Guaiacol Benzoate (Benzosol), small, white crystals, almost insoluble in water, and almost without taste or odour. Dose ·2 to ·8 gm. (3 to 12 grains).

Guaiacol Cinnamate (Styracol), white crystals, insoluble in water and tasteless. Dose ·3 to 1 gm. (5 to 15 grains).

Guaiacol Salicylate, white crystals, insoluble in water. Dose ·3 to 1 gm. (5 to 15 grains).

Guaiacol Camphorate (Guacamphol), white, tasteless, and odourless needles, insoluble in water. Dose ·2 to 1 gm. (3 to 15 grains).

Guaiacol Albuminate (Histosan), a light brown powder, with slightly aromatic taste and smell. Insoluble in water and dilute acids, easily soluble in alkalies. Dose ·5 gm. (8 grains). For children, a 5 per cent syrup is made, the dose of which is from a teaspoonful to a dessertspoonful.

Methylene Guaiacol (Palmoform), a colourless, tasteless, and odourless powder, formed by the

action of formic aldehyde on guaiacol. Dose ·5 to 1·0 gm. (8 to 15 grains).

Ethyl-glycol-guaiacol (Monotal) is a colourless oil, with a slightly aromatic taste, insoluble in water.

Guaiacol Valerianate (Creosote-Eosote) is a colourless fluid, insoluble in water. The dose is ·2 gm. (3 min.) in capsules or emulsion.

The soluble compounds are :—

Guaiacol-glycerin-ester (Guaiamar), a dry, white, crystalline powder, with a bitter and at the same time aromatic taste. Dose, ·2 to 1 gm. (3 to 15 grains) ; externally as a 25 per cent ointment in lanoline.

Guaiacol-potassium-sulphonate (Thiocol) in colourless crystals. Dose 1 gm. (15 grains) from three to ten times in twenty-four hours. A 10 per cent solution in syrup is known as **Sirolin.** Dose, 1 teaspoonful to 1 tablespoonful, three or four times a day.

These compounds, which are mainly used in cases of phthisis and as intestinal antiseptics, no doubt depend for their efficiency upon the ease with which guaiacol is liberated in the body. From this point of view, according to the experiments of Knapp and Suter,* who estimated the amount decomposed by the increase of conjugated sulphate in the urine, the cinnamate is the most efficacious. It is not probable, however, that the cinnamic acid portion of the molecule produces much effect on the tuberculous

* *Arch. f. exp. Path. u. Pharm.*, i., p. 332, 1903.

process. The main objection to the cinnamate is its somewhat high price. The carbonate, which liberates 50 per cent guaiacol, is much cheaper, though not quite so efficient. The potassium sulphonate (thiocol), though possessing a low toxicity, is probably the feeblest form in which guaiacol can be given. It is the form in which, as has been noted above, guaiacol is excreted, and it is not, therefore, surprising that it has been shown experimentally to pass through the body unchanged. The camphorate is intended for checking night sweats in phthisis.

Monotal is used externally only; the crystals melt into a colourless oil when warmed by the hand, and can be rubbed into the skin. The amount used per diem may be 4 or 5 gm. (60 to 75 grains). It is mainly employed to relieve local pain or inflammation. None of the guaiacol compounds have, as a rule, any unpleasant bye-effects. Very occasionally, a special idiosyncrasy may be noted in a patient, and loss of appetite or diarrhœa have in rare cases been found to follow the use of one or another of the compounds.

2. Cinnamic Acid and its Derivatives.

These preparations, although they have a certain vogue on the Continent, have never been extensively used in this country. As long ago as 1890, Landerer, in Stuttgart, was experimenting with solutions of cinnamic acid, but in 1893 he substituted cinnamate of sodium, which he found more suitable owing to

its greater solubility. This he injected intravenously, in amounts not greater than ·025 gm. The solution he used is known as **Hetol**. The known physiological action of this substance and of its derivatives is limited to the production of an absolute and relative polynuclear leucocytosis, and though other actions have been suggested to explain its apparently good results in certain clinical cases, there is no experimental basis for these conjectures. The technique of the injections is as follows:— ·001 gm. of hetol is injected intravenously every third day, and on every third injection the dose is increased by 1 mgm. till ·01 gm. is reached. The increments are then raised to 2·5 mgms. every third injection, till the maximal dose of 20 to 25 mgms. is reached. The strength of the solution is 1 per cent until 10 mgms. are given; it is then raised to 5 per cent. The injections are stopped during the menstrual periods in women, and the increase in dosage is stopped in cases where the oral temperature is above 99·5° F. (37·3° C.).* Modifications of this method have been made by various clinicians; notably in Spain, where Herrero† and others have injected large doses intramuscularly, beginning with ·03 gm., and gradually raising the amount to ·6 or ·7 gm.

In this country Drage has employed a 10 or 11

---

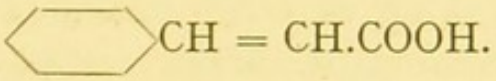
* An account of this treatment, with references to the original papers, will be found in *Guy's Hospital Reports*, vol. lviii., p. 31, 1903.

† *Lancet*, 1909, i., p. 413.

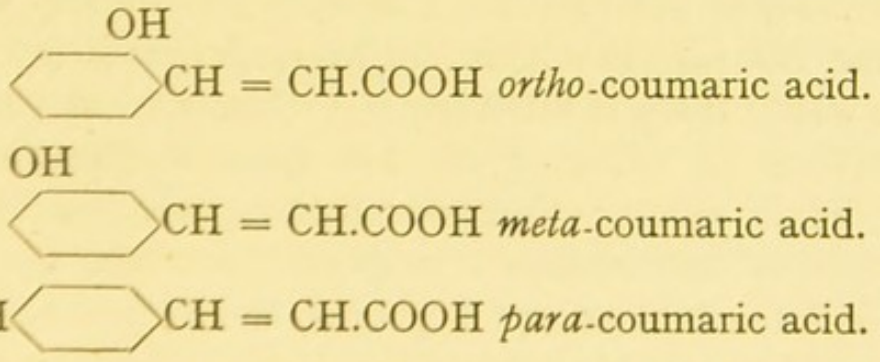
per cent solution of cinnamate of sodium, of which he injects from 15 to 30 min. (1 to 2 cc.) every week hypodermically. In some cases larger doses (4 cc. = 60 min.) have been given in this way.*

Drage and Morgan have also used other derivatives of cinnamic acid.

To explain the relative position of these bodies, a short account of their chemical structure is necessary. Cinnamic acid is a benzene derivative, the corresponding aldehyde of which is the main principle found in oil of cinnamon. Its structure is thus shown :—



If a hydroxyl (OH) group is introduced into the benzene ring, those acids known as the coumaric acids are produced, which are isomeric and only differ in the position of the OH group relatively to the other side-chain.



ortho-coumaric acid.

meta-coumaric acid.

para-coumaric acid.

All these bodies produce leucocytosis, and are antiseptics; in the latter quality the *ortho* compound is the most powerful.

* *Lancet*, 1902, ii., p. 66 and 1903, i., p. 1441.

In practice Drage recommends a 22 per cent solution of *ortho*-coumarate of sodium in water, of which he injects 1·5 cc. (25 min.) hypodermically, not more than three times a week. In addition he gives by the mouth either ·06 cc. (1 min.) cinnamic aldehyde in a capsule three times a day, or else ·3 gm. (5 grains) *tylmarin* (acetyl-coumaric acid): either drug should be given after food.

It seems certain that some cases of phthisis improve while taking a course of sodium cinnamate or some similar body; in few of the reported cases, however, is it shown that improvement was due solely to the drug, as other measures were usually adopted concurrently. Many authors (including Dr. Drage) only publish one or two isolated cases, and a general survey of all recorded cases shows that the results are no better on the whole than those obtained by ordinary sanatorium treatment.

As a rule, injections of hetol do not produce any unpleasant symptoms. Landerer and others, however, consider that they are contraindicated in cases in which there is a tendency to hæmoptysis; those patients in whom there has been long-continued pyrexia, severe digestive disturbances, or where intestinal tuberculosis is suspected, or where there is ulcerative tuberculous laryngitis, should not be thus treated unless confined to bed.

Various authors have in certain cases noted fever, restlessness, and cyanosis, cold sweats, small pulse, mental confusion, and other nervous symptoms. Loss of weight sometimes occurs, and the

intramuscular injections are occasionally painful (O. Seifert).

3. Cellotropin.

Chemically this body is a compound of benzoyl with the glucoside arbutin. It occurs in the form of a white, tasteless, crystalline powder, only slightly soluble in cold water, but easily soluble in alcohol. The dose is ·3 to ·5 gm. (5 to 8 grains). It is said to diminish nitrogenous excretion, and to increase in some way the specific resistance of the body to tubercle, but it is admittedly useless in advanced cases. Its high price, and the difficulty of proving that it is of any value, even in early cases, will tend to prevent its general use in phthisis.

4. Vanadic Acid and its Derivatives.

Vanadium is a metal found in small quantity in iron ores, and belonging to the same group as antimony and bismuth. It forms five oxides, analogous to the oxides of nitrogen, the highest of which, vanadium pentoxide V_2O_5 or vanadic oxide, dissolves in the stronger acids, forming coloured solutions (red or yellow) which crystallize out as vanadates. There are a number of acid and neutral salts of vanadic acid, analogous to those of phosphoric acid; in medicine, solutions of vanadic acid and of the metavanadate of sodium ($2\,Na_2O.V_2O_5$) alone are used. There is also on the market a body named vanadine of Helouïs, the composition of which is uncertain.

Metavanadate of sodium is a colourless, crystalline salt, the dose of which is 1 to 5 mgms. (approximately $\frac{1}{60}$ to $\frac{1}{12}$ grain) per diem. It may be given in solution or in pilules, half an hour before meals. The drug should be administered for periods of four to eight days, and then omitted. Hypodermically the dose is 1 mgm. ($\frac{1}{60}$ grain).

Vanadic acid is given in doses of 1 to 1·5 mgm. (approximately $\frac{1}{60}$ to $\frac{1}{40}$ grain) per diem; or hypodermically ·5 mgm ($\frac{1}{120}$ grain) may be given.

The introduction of vanadium compounds into medicine was due to the fact that they are capable of acting as oxygen carriers, and thus oxidizing organic matter. It was thought, therefore, that they might be able to influence favourably the tissue respiration and promote oxygen exchange. When tested physiologically, they were found, however, to be very toxic to laboratory animals (rabbits and dogs), causing digestive disturbances, with vomiting and diarrhœa, and subsequently paralyzing the medullary centres. Some observers have found that they possess a digitalis-like action on the heart and blood-vessels, but this has not been noticed by all. It has not, however, been possible to show that vanadium compounds produce any increased tissue respiration experimentally.

Laumonier,* to whose excellent account the reader is referred for further details, attributes the good

---

* *Op. cit.*, p. 66.

results which some writers describe, especially in cases of early phthisis, entirely to a local action on the gastric and intestinal tract. The improvement in appetite and increase in weight, he considers are due to the slight stimulant action of the drug, which, when pushed, may go on to irritation, with diarrhœa and vomiting. It lasts only so long as the drug is given, and many patients soon acquire a toleration, after which the effect of therapeutic doses is *nil*. The oxidizing properties of vanadic salts led to the belief that they might act as antiseptics, but this property is so slight as to be negligible for practical purposes.

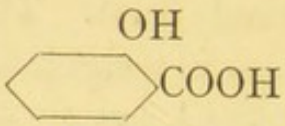
II.—REMEDIES FOR ACUTE RHEUMATISM.

The modern treatment of acute rheumatism is summed up in the one word "salicylates," and the drugs which have recently been introduced as remedies for this condition are consequently all modifications of salicylic acid. For practical purposes they may be separated into two classes, those intended for internal use, and those intended for external application.

1. Internal Remedies.

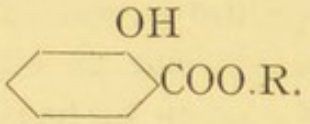
The appearance of these on the market is due to a desire to find some derivative of salicyl which, while therapeutically equally effective, shall not produce the unpleasant bye-effects which are not infrequent after a large dose of the ordinary salicylates.

The structure of salicylic acid shows that it is *ortho*-oxybenzoic acid

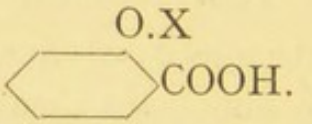


and it will consequently be possible to modify this substance in three ways :—

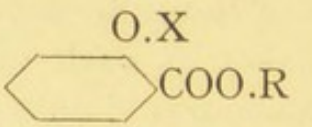
1. The hydrogen of the carboxyl (COOH) group may be replaced by a radicle " R " thus :—



2. The hydrogen of the hydroxyl (OH) group may be similarly replaced by a radicle " X " :—



3. Both these hydrogen atoms may be replaced :—



Group 1.—The bodies in this group are " ethers " or " esters " of salicylic acid, i.e., bodies in which an organic radicle takes the place of the hydrogen in the acid group COOH. The simplest is **Salol,** in which phenyl (C_6H_5) is the substituting radicle. The others are :—

Diaspirin, a powder easily soluble in alcohol, but almost insoluble in water. It produces diaphoresis. The dose is ·5 to 1 gm. (8 to 15 grains) several times daily.

Novaspirin, the methylene-citric-acid ester, is a white, almost insoluble powder, with a slightly acid taste and no smell. It is soluble in alcohol. The dose is ·5 to 1 gm. (8 to 15 grains). It is hardly at all diaphoretic.

Rheumatin, the salicyl-quinine ester, is a colourless, almost insoluble powder, the dose of which is 2 to 6 gm. (30 to 90 grains) per diem in divided doses.

Salacetol, the acetol ($CH_2.COCH_3$) ester, is a white, insoluble powder. The dose is 2 to 3 gm. (30 to 45 grains) every morning.

Salimenthol, the ether with menthol, is an oily, light yellow liquid, insoluble in water but easily soluble in alcohol and oils. It may be given in capsules containing ·25 gm. (4 grains) or less, three to six times daily.

Salophen, the acetyl *para*-amidophenol ether, is a white, almost insoluble powder, without taste or smell. It is not decomposed by acids or pepsin. The dose is ·5 gm. (8 grains).

Group 2.—In this group only one example is found, namely **Aspirin** or acetyl salicylic acid. $C_6H\begin{cases}O.CH_3CO\\COOH\end{cases}$ It consists of small, white needles only very slightly soluble in water, and incompatible with alkalies. The dose is ·5 to 1 gm. (8 to 15 grains), but much larger quantities are given.

Group 3.—Contains four somewhat complicated bodies, namely :—

Aspirophen, or acetyl-salicylic-acid amidophenacetin, is a fine, crystalline powder, easily soluble in hot water, but less soluble in cold. The dose is 1 gm. (15 grains) or less several times daily.

Benzosalin, or the methyl-ester of benzoyl-salicylic acid, is a white, crystalline substance, practically insoluble in water, and not decomposed in the stomach. The daily dose is 2 to 5 gm. (30 to 75 grains).

Methyl Rhodin, Methyl Aspirin, or acetyl salicylic methyl ester, is a colourless, crystalline substance, insoluble in water, and undecomposed in the stomach. The dose is the same as that of aspirin.

Diplosal consists of the salicyl ester of salicylic acid, and is a colourless, crystalline powder, practically insoluble in cold water and dilute acids, but decomposed by dilute alkalies. The dose is 3 to 6 gms. (45 to 90 grains) in twenty-four hours either in cachets or ·5 gram tablets.

The most important of these substances is no doubt aspirin or acetyl-salicylic acid, which has been very largely used instead of the ordinary salicylate of soda. It is said not to produce unpleasant toxic symptoms so readily as do the salicylates; as it is not decomposed in the stomach, it is not likely to produce any local digestive disturbances there, and in this respect it resembles methyl aspirin, benzosalin, aspirophen, and salophen. The toxic symptoms produced by the salicylates after absorption, such as tinnitus and deafness, are

of course produced in proportion to the free salicyl ions circulating in the body. All active salicyl compounds, therefore, will be liable to produce these symptoms in susceptible persons, according as they are efficacious as drugs. It will be noted that novaspirin and diaspirin are not chemically at all similar to aspirin in structure, as they belong to the first and not the second group. Novaspirin has been rather largely employed, because it seldom disturbs digestion. It contains 62 per cent only of salicylic acid, and is not a powerful preparation.

2. External Remedies.

Some of those already mentioned among internal remedies are also used externally. There are no examples of the second and third chemical groups which were mentioned in the first class. All the external applications are salicylic acid esters, in which the second radicle replaces the hydrogen of the carboxyl.

Group 1.—**Methyl-salicylate,** or oil of wintergreen, is the typical external salicyl preparation, but its strong, penetrating odour renders other bodies occasionally more serviceable.

Glycosal is the monoglycerin ester of salicylic acid. It is miscible with glycerin, and soluble in alcohol and hot water, but hardly at all in cold water. It may be employed as a 10 per cent ointment or 20 per cent paint. It may produce itching, sweating, and symptoms of salicylate poisoning. It has been employed internally, but is not suitable for this purpose, owing to its unpleasant taste.

Mesotan. This, the methoxy-methyl ester, in spite of its high price, is a largely used preparation. It is a liquid, insoluble in water, but soluble in oil and the usual organic solvents. It possesses hardly any odour. It easily liberates formaldehyde, and so is liable to cause considerable dermatitis. Various methods have been recommended to obviate this unpleasant result. The most usual is to paint the skin lightly with a mixture of equal parts of olive oil and mesotan, and then cover it with a piece of flannel or wool. The application should be stopped as soon as the skin becomes reddened. Some employ ether or absolute alcohol as the diluent, but vaseline is to be avoided. Meisser* recommends a mixture of mesotan 30, ichthyol 10, chloroform 20, ol. olivæ 40 ; or mesotan 20, ichthyol 20, ol. olivæ 60. Mesotan probably owes its popularity to the fact that it is odourless and expensive ; a 15 per cent ointment of salicylic acid in lanoline is quite as efficacious.

Salen is a mixture of methyl and ethyl glycolic esters. These bodies are crystalline solids which liquefy on being mixed. The resulting liquid is soluble in ether, alcohol, castor oil, and a mixture of chloroform and olive oil. It possesses no odour. A 33·3 per cent ointment is sold under the name of **Salenal.**

Salimenthol, already described, may be used externally as a 25 per cent ointment (**Samol**).

---

* q. Seifert, iii., 7.

Salit, the borneol ester, is an oily fluid, insoluble in water, slightly soluble in glycerin, and easily soluble in alcohol, ether and oils. It may be mixed with equal parts of olive oil, and ½ to 1 teaspoonful of the mixture may be painted on to the skin, or rubbed in and covered with cotton-wool twice daily. It is liable to set up dermatitis, especially if the skin is not clean. The part to be treated should therefore be first well washed with soap and water and alcohol.

Salocreol, a compound of salicylic acid and creosote, is a brown, oily fluid, easily soluble in alcohol, but insoluble in water. It has a disagreeable odour, but is said to be an efficacious preparation. It is to be rubbed in pure.

Spirosal, the monoglycolic ester, is an oily fluid, miscible in all proportions with alcohol, ether, and chloroform. One half to one teaspoonful of the pure substance, or of a mixture with an equal part of alcohol, may be rubbed in locally, the place being then covered up with cotton-wool or flannel. It may produce dermatitis and, if rapidly absorbed, the ordinary symptoms of salicysm.

III.—REMEDIES FOR WHOOPING-COUGH.

Of the numerous drugs which have at one time or another been recommended for the treatment of whooping-cough, few have survived, for any very lengthy period, the ordeal of clinical experience. Some are but substitutes for older remedies, such as aristoquin, quinaphenin, and euquinine, the value of which will merely depend on the value of the drug

they represent, namely quinine. Their character and properties have already been described (*vide* Chap. vii., p. 207), and they need not be further dealt with individually. The main disadvantage of quinine as a drug for young children is its bitter taste, which is difficult to conceal. Otherwise it is undoubtedly somewhat valuable in these cases. Quinaphenin and euquinine, being insoluble, are tasteless.

Other remedies are merely mixtures with more or less attractive trade names, such as **Pyrenol,** which is said to contain benzoic acid, thymol, sodium benzoate, and sodium salicylate.

A third class of bodies is that comprising antipyrin derivatives and other drugs of the antipyretic group. Of these **Eulatin** is the amidobrombenzoate of antipyrin, a white powder with an acid taste and slight odour. It may also be obtained in tablets. Friedmann* reports favourably on this drug, which he gives in doses of ·1 to ·5 gm. (1½ to 8 grains) every three or four hours, either as a powder or as an emulsion with raspberry syrup. Baedeker† advises that full doses should be given, such as twelve ¼-gram tablets daily to a child of four years of age; and six to ten to a child of eighteen months. It apparently has no harmful effects, and is probably an improvement on antipyrin for the treatment of this condition. Tussol, on the other hand, presents no special advantages (*vide* p. 235). Citrophen and

* *Med. Klin.*, iv., 43, 1908.
† *Ther. Monatsh.*, xxiii., 9, Sept., 1909.

phenocoll (*vide* chap. vii., p. 221 and p. 223) are phenacetin derivatives, which have the disadvantage of a somewhat well-marked toxicity. They cannot, therefore, be recommended for children.

It is a well-established clinical fact that belladonna in full doses is by far the most effective drug in the majority of cases of whooping-cough occurring in children ; and it is perhaps on this account that no substitutes, in the true sense, for belladonna have been introduced. A drug, however, which is chemically related to atropine, and which is most interesting from the pharmacological point of view, has recently been recommended for this condition, and possibly deserves a wider trial than it has yet received. This drug is known only by its chemical name of **Methylatropine Bromide,** and consists of white crystals, easily soluble in water, the dose of which internally is 1 to 2 mgm. ($\frac{1}{60}$ to $\frac{1}{30}$ grain). Chemically, it is atropine, to which one atom of bromine and one methyl (CH_3) group have been added to the nitrogen, thus altering the valency of the latter element from a triad to a pentad condition. Various changes in the physiological action of the drug are brought about by this means, one of which is a considerable drop in toxicity. It has been employed as a substitute for morphine, owing to its sedative action ; and in one case, which the present writer had an opportunity of observing some years ago, it had a distinct effect, comparable to that of opium, on the sugar excretion of an elderly glycosuric.

As regards whooping-cough, Bolgar* reports good results with a mixture containing antipyrin and methylatropine bromide; the dose of the latter for a child of five was about ·0006 gm. Subcutaneous injections of methylatropine bromide may be made with a solution containing ·05 gm. of the alkaloid ($\frac{4}{5}$ grain) in 10 gm. (about 150 minims) of aqua laurocerasi (B.P.). The dose for an adult is from one quarter of this amount up to the whole; and for children the smaller quantity may be considered a maximum. Aronheim† suggests the following prescription for cases of whooping-cough :—

℞	Methylatropinæ Bromidi	·03 – ·05 gm. (gr. $\frac{1}{2}$–$\frac{3}{4}$)
	Phenazoni	·5 gm. (gr. viij)
	Aq. Chloroformi	ad 200 cc. ($\bar{3}$vij)

The dose is one tablespoonful.

Two derivatives of one of the alkaloids found in opium have also been introduced as specifics for whooping-cough. These are **antispasmin** and **narcyl.** The former is narceine sodium, combined with sodium salicylate, and is a white powder, easily soluble in water, containing half its weight of narceine. The dose is ·01 to ·2 gm. ($\frac{1}{6}$ to 3 grains) three times daily. The latter is narceine-ethyl hydrochloride, and consists of white, glistening crystals, soluble in 120 parts of water, and easily soluble in ether and chloroform. The dose is ·06 gm. (1 grain) by the mouth, or ·02 gm.

* *Aerztl. Zentralzeitung*, xvi., No. 14–15, April, 1904.

† *Berlin. Klin. therap. Woch.*, No. 28, p. 756, 1904.

($\frac{1}{3}$ grain) subcutaneously. Debono* recommends a syrup containing ·03 gm. ($\frac{1}{2}$ grain) to the half ounce. Children from two to four years of age can take 1 to 3 drachms in twenty-four hours; those of four to seven years, 4 to 5 drachms; and those of seven to fifteen years, $\frac{1}{2}$ to 1 ounce. These bodies appear to have a mild morphine-like action, and to present no particular therapeutic advantages. Narcyl is said to act directly on the vagus nerve-endings.†

Bromoform is a sedative of undoubted pharmacological activity, and was at one time largely used in Germany and elsewhere. As its name implies, it is homologous with chloroform, and has the formula $CHBr_3$. Physically it is a colourless, mobile liquid, with a sweetish taste and somewhat characteristic odour. It is unstable, and liberates bromine under the influence of light, the liquid then assuming a yellow colour. Its specific gravity is high, nearly three times that of water, in which it is only slightly soluble. The dosage has been variously stated as from $\frac{1}{8}$ to 3 minims, or even 5 minims several times daily.

It appears certain from a consideration of the reported cases, which are by now fairly numerous, that bromoform is indeed an efficacious remedy, and its general adoption has only been prevented by the comparative frequency with which cases of serious poisoning have occurred. Waterhouse,‡ in an

* *Therap. Monatsh.*, No. 10, p. 539, 1905.
† Noé, *Gaz. des Hôpitaux*, lxxxiii., 35, 1905.
‡ *Bristol Med.-Chir. Jour.*, xxviii., 108, p. 127, 1910.

excellent review of the literature, has collected forty-eight cases, five of which were fatal, in addition to two observed by himself, both of which fortunately recovered. He classifies the cases of poisoning under three heads: (1) Those in which by intent or accident a large amount has been taken at one time; for instance, children who have taken large doses surreptitiously owing to their liking for its sweet taste; (2) Those in which toxic symptoms have followed on the last dose in the bottle; (3) Those in which apparently only an ordinary dose has been taken. The cases grouped under the second heading arise owing to the difficulty of dispensing bromoform in a mixture. It is heavier than mucilage, and sinks to the bottom of the bottle if prescribed in this way, and even spirit and water dispensed *secundum artem* is not, according to Waterhouse, a satisfactory medium. He found tincture of senega, as recommended in Martindale and Westcott's *Extra Pharmacopœia*, the best suspender, and employed the following prescription:—

℞	Bromoformi	♏xliv	Syr. Aurant.		ʒiv
	Tr. Senegæ	ʒiiiss	Aq.	ad	ʒxliv
	Sp. Vini Rect.	ʒj			

A drachm dose of this mixture contains nearly one minim of bromoform, and was ordered to be taken thrice daily. A case of poisoning, however, occurred, which was apparently due to the decomposition of the bromoform and liberation of bromine.

Squire (*Companion to the British Pharmacopœia*)

recommends that the drug be dissolved in almond oil, and then put into capsules or made into an emulsion.

The symptoms of bromoform poisoning are coma, subnormal temperature, slight cyanosis, and loss of reflexes. The pupils are contracted in the lighter cases, and dilated when the coma is more intense. Generally, the condition is very similar to that induced by chloroform. The largest dose after which recovery has taken place appears to be between 5 and 7 gm. (child, aged 2½); but less than a gram has proved fatal in a child of about the same age.

In spite of its value as a remedy, the record of disasters after bromoform should make the practitioner extremely cautious in prescribing it; accidents of an alarming nature have occurred, even when all due precautions have been taken, and considering that there are other equally efficacious and less dangerous methods of treating the disease, the question whether this remedy can be justifiably employed must be regarded as open to very serious doubt.

Bromatol is an emulsion of bromoform in cod-liver oil, in which each cubic centimetre (about 20 minims) contains 1 drop (⅛ minim) of the drug.

Anæsthesin has been already described as a local anæsthetic (p. 176). It has also been used to allay vomiting from various causes, including whooping-cough. Reiss* recommends doses of ·5 gm. (8 grains)

Therap. der Gegenw., N.F., vii., 10, p. 458, 1905.

in cachets, and says that compressed tablets should never be employed. It is, of course, a merely symptomatic form of treatment, and its efficacy depends on its local anæsthetic effect on the gastric mucosa.

Fluoroform (a 2·8 per cent solution of which is known as fluoroformol) has also been employed apparently with success. Stepp* states that it is absolutely non-toxic, and may be given to the youngest and most delicate infant with safety. It is devoid of taste and odour, but produces a slight burning sensation in the throat after it has been swallowed. The dose is a teaspoonful to a dessert-spoonful every hour; full doses are necessary. Eissier† gives one drop to small children after every paroxysm, and as these become less frequent the dose may be increased, not more than 100 drops being taken in twenty-four hours. For children from two to four years the maximum is 30 gms. (about 1 oz.) a day in teaspoonful doses. It is an expensive remedy: three to four weeks' treatment for an adult is estimated to cost twenty to thirty shillings.

Antitussin is an external remedy, consisting of vaseline 10 parts, anhydrous wool fat 85 parts, and difluordiphenyl 5 parts. A piece "the size of a nut"‡ is directed to be well rubbed into the neck or chest once a day. The method appears to be

---

* *Ther. Monatsh.*, xviii., 11, 1904.

† *Lancet*, 1907, vol. ii., p. 1351.

‡ Rabner, *Münch. med. Woch.*, lii., 25, 1905.

cumbrous, and, *prima facie*, unlikely to be particularly successful.

IV.—REMEDIES FOR GONORRHŒA.

The main disadvantage of the balsams and volatile oils in the internal treatment of gonorrhœa is their irritant action on the gastric mucosa and renal epithelium. Both the terpenes—$(C_5H_8)_2$—which are the chief constituents of oil of copaiba and oil of cubebs, and to a less extent the terpene alcohols, such as santalol—$(C_{15}H_{25})OH$,—(which forms 90 per cent of oil of sandalwood) are liable to produce nausea, vomiting, and symptoms of renal inflammation.* Even when applied externally the balsams may set up renal disturbances, such as albuminuria.†

The object of the newer antigonorrhœic preparations is to obviate these unpleasant symptoms. They have not been shown to be more active than the older preparations in eradicating the source of the disease, and the very generally expressed opinion of those who have tried them is, that they should always be given in conjunction with efficient local treatment and careful regulation of the diet.‡ The principal preparations (one of which may well supersede the use of the ordinary oil of sandalwood and the balsams in private practice) are :—

1. **Gonosan.**—This is a mixture of pure East

* Vieth and Ehrmann, *Deut. med. Woch.*, xxxii., No. 2, 1906.

† Allan, *The Hospital*, April 13, 1907, p. 35.

‡ *Vide* Boehme's résumé in *Schmidt's Jahrbücher*, 298, p. 78; 300, p. 49; 1908: 294, p. 182; 1907, etc.

Indian santalol (60 per cent) with kawa (20 per cent), a resin extracted from the root of *Piper methysticum*. This substance has a local anæsthetic action on the gastric mucosa,* thus preventing the pain and discomfort sometimes set up by the santalol. Nigoul† thinks it also acts as a sedative to the nerve centres in the lumbar cord, and Varges‡ credits it with contributing to the bactericidal action of the preparation. The dose is ·3 gm. (5 grains) in capsules, three times daily, or oftener. The gonococci have been eliminated from the urine in ten days, according to Varges; but Saar§ found that in 80 per cent of the cases, gonococci were still present after several weeks where no efficient local treatment had been carried out in addition.

Urogosan is a mixture of gonosan and uramine (hexamethylene-tetramine), containing ·3 gm. (5 grains) of the former to ·15 gm. (2½ grains) of the latter in capsules. It is specially intended for cases complicated by cystitis, or when posterior urethritis is present.

Santyl is the salicylic acid ester of santalol, and is non-irritant to the gastric mucosa. It is almost devoid of taste and smell, contains 60 per cent of the volatile oil, and may be given in doses of 30 drops (6 grains) three times a day, best in coffee or milk; but may also be obtained in capsules. It may be combined with uramine.

---

* Sternberg, *Alleg. med. Zentralzeitung.*, lxxvi., 15, 1907.
† *Leipsig Mon. Schr.*, No. 3, 1907.
‡ *Med. Klin.*, No. 45, 1905.
§ *Münch. med. Woch.*, lii., 46, 1905.

Arhovin is stated by the makers to be a chemical compound; but it appears more probably to be a mixture of benzoic acid ethyl ester, thymol, and diphenylamine. It is a yellow, oily fluid, with an aromatic odour, and a cool, burning taste, insoluble in water, and best given in gelatin capsules containing ·25 gm. (4 grains). A 1 to 2 per cent solution in oil may be used locally, and bougies are also prepared containing ·05 gm. each.

V.—REMEDIES FOR FUNCTIONAL NERVOUS DISORDERS.

The established value of valerian as a remedy for certain disordered conditions of the nervous system, coupled with the increasing numbers of such cases which come under medical treatment, has led the enterprising manufacturer of new drugs to furnish this domain of pharmacy with several well-advertised preparations. When, however, the matter is judicially considered, there seems very little reason for these expensive synthetic products, as the ammoniated tincture of valerian (B.P. and U.S.P.) or one of the other official preparations of the root are perfectly efficient, and produce no undesirable bye-effects. The principal substances found in valerian root are two terpenes, borneol, and esters of formic, acetic, and valerianic acids, which are present in the volatile oil. It is to this oil that the efficacy of the drug is due. Metallic salts of valerianic acid are inactive. The synthetic valerian derivatives are :—

1. **Valyl,** the di-ethylamide of valerianic acid, a clear, colourless fluid, with a burning taste and characteristic odour. It is sold in gelatin capsules, one or two of which may be taken several times a day.

2. **Bornyval,** the iso-valerianic acid ester of borneol, a clear, colourless liquid, with an aromatic odour and taste slightly resembling those of valerian. It is insoluble in water, and sold in capsules; they may be taken in the same way as valyl.

3. **Validol,** the menthol ester of valerianic acid, which contains also 30 per cent free menthol. It is a colourless fluid with a mild, pleasant odour, and refreshing taste. The dose is 10 to 15 drops. An effervescing form is also sold.

4. **Valisan,** the bromo-isovalerianic ester of borneol, a clear, colourless fluid, with a slightly aromatic odour and very little taste. It is insoluble in water, and sold in gelatin capsules, containing ·25 gm. (4 grains) of the drug. One to three may be taken several times daily.

INDEX

2763.10 JOHN WRIGHT AND SONS LTD., PRINTERS, BRISTOL.

THE FIFTH IMPRESSION.

53 *Illustrations. Bevelled Boards, Burnished Top,* 21/- *net.*

AN INDEX OF TREATMENT. Edited by ROBERT HUTCHISON, M.D., F.R.C.P., Physician to the London Hospital; and H. STANSFIELD COLLIER, F.R.C.S., Surgeon to St. Mary's Hospital.

Nearly 1,000 *Pages.* 28*th Year.* 8/6 *net. Stereoscopes,* 2/- or 2/6 *net.*

Illustrated with 52 full-page Plates—Coloured, Black and White, and Stereoscopic—and 108 Illustrations in the text.

MEDICAL ANNUAL, A YEAR BOOK OF TREATMENT AND PRACTITIONER'S INDEX. Comprising a General Review of Medicine and Surgery; Dictionaries of Modern Therapeutics and of Treatment; Together with Papers of Special Interest.

Now Ready. Crown 8*vo. With numerous Diagrams.* 5/6 *net.*

THE PRESCRIBING OF SPECTACLES. By A. S. PERCIVAL, M.A., M.B., Senior Surgeon to the Eye Infirmary, Newcastle on-Tyne. Author of "Optics," "Practical Integration," etc.

This book describes the practical methods of determining errors of refraction and errors of muscular balance, and gives clear directions for Prescribing Spectacles for their treatment. Dr. Tscherning's latest evaluation of the optical constants and the latest results of Dr. Duane's research work on accommodation are included. The last fifty pages give the mathematical solution of most of the optical problems, as well as five tables that are frequently required in dealing with the subject.

Now Ready. Fully Illustrated. Demy 8*vo.* 10/- *net.*

With 3 *Coloured Plates and numerous Illustrations in the Text, many of which are reproductions from the Author's sketches.*

DISEASES OF THE COLON, AND THEIR SURGICAL TREATMENT. (Founded on the Jacksonian Essay for 1900.) By P. LOCKHART MUMMERY, F.R.C.S. Eng., B.A., M.B., B.C. Cantab., Jacksonian Prizeman and late Hunterian Professor, Royal College of Surgeons; Senior Assistant Surgeon, St. Mark's Hospital for Cancer, Fistula, and other Diseases of the Rectum; and Senior Surgeon to Out-Patients, The Queen's Hospital for Children, London.

MEDICAL WORKS

JOHN WRIGHT & SONS LTD., PUBLISHERS, BRISTOL.

Prices, subject to alteration : 3/- to 6/- each.
With Explanatory Notes.
Full particulars on application.

PAPIER MÂCHÉ CASTS OF HUMAN ANATOMY (carefully Coloured by Hand), Prepared under the direction of CHARLES W. CATHCART, F.R.C.S., Surgeon Royal Infirmary, Edinburgh.

Now Ready. Two Volumes, 50/- net.
With 994 Beautiful Illustrations in the Text, and 20 Full-page Plates.

URGENT SURGERY. By FÉLIX LEJARS, Professeur Agrégé à la Faculté de Médicine de Paris ; Chirurgien de l'Hôpital Saint-Antoine. Translated from the Sixth French Edition by W. S. DICKIE, F.R.C.S. Eng., Surgeon North Riding Infirmary, Con. Surg. Union Infirm., Middlesbrough ; Con. Surg. Eston Hospital.

This unique work is not intended solely, or even perhaps chiefly, for the Surgeon : but will be found invaluable to the conscientious General Practitioner, who is at any time liable to be confronted by emergencies demanding immediate surgical interference.

Fifth Edition. Largely re-written. 12/6 net.
With 334 Illustrations and Plates, all re-drawn and improved for this Edition.

PYE'S SURGICAL HANDICRAFT. A MANUAL OF SURGICAL MANIPULATIONS, MINOR SURGERY, AND OTHER MATTERS CONNECTED WITH THE WORK OF HOUSE SURGEONS, SURGICAL DRESSERS, ETC. Edited and largely re-written by W. H. CLAYTON-GREENE, B.A., M.B., C.M. CAMB., F.R.C.S., Assistant Surg. and Surg-in-Charge of Out-patients, St. Mary's Hospital ; Surgeon French Hospital.

With the addition of Special Chapters concerning ANÆSTHESIA : Joseph Blumfeld, M.D. DISEASES OF THE EAR, NOSE, THROAT, AND LARYNX, AND HEAD INJURIES : H. W. CARSON, F.R.C.S. DISEASES OF THE EYE ; Leslie Paton, B.A., B.C., F.R.C.S. TREATMENT OF THE TEETH ; Norman G. Bennett, M.A., M.B., B.C., L.D.S. Eng. POISONING AND URINE TESTING : William Henry Willcox, B.Sc., M.D. X-RAYS AND THE TAKING OF SKIAGRAMS : G. Allpress Simmons, M.D., B.S.